THE FIFTH REVISION OF THE DECLARATION OF HELSINKI AND THE ETHICAL LANDSCAPE OF MEDICAL RESEARCH

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DECLARATION

This thesis and the data presented within it are entirely the results of my own efforts except where stated otherwise. This work contains no material that has been accepted for the award of any other degree or diploma in any university or tertiary institution and, to the best of my knowledge, contains no material previously published or written by another person, except where stated in the text.

Dr Robert Victor Carlson

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Three publications arose during the course of this thesis; two of which (see Chapters 2 and 4) were co-authored by myself and my two supervisors. First, I am grateful for their permission to publish this material (and the material in Chapter 5) – a regulatory requirement of the university. Although the text of the manuscripts represents my own work, without their supervisory guidance and advice neither the thesis chapters or the publications could ever have been completed.

I would like to thank Professor Andreas Frewer (University of Hannover, Germany) and Professor Ulf Schmidt (University of Kent) for inviting me to

present the material from Chapter 4 at a conference in October, 2004; an invitation which subsequently enabled publication of the material as a chapter in the book that resulted from the conference proceedings.

In Chapter 5, the work on the Declaration of Helsinki in its 3 official languages, there are a number of people, in addition to my supervisors, that I need to thank for assistance both in making this work sufficiently coherent for a thesis chapter and in enabling this material to be published. My knowledge of French (a legacy of being born and raised in bilingual Canada) was sufficient, on reading the French version of the Declaration of Helsinki, to realise that there were important differences between the two documents. However, my fluency in French would not have been sufficient to carry this work forward in a robust academic manner. Additionally, this raised the question of whether there were also differences in the Spanish version and my knowledge of Spanish, although better now, was almost non-existent at the time. Without the additional contribution of my colleagues Dr. Nadja van Ginneken and Dr Luisa Pettigrew, fluent in French and Spanish respectively (as well as English), this work could not have progressed. Their painstaking work in helping me compile a catalogue of the differences between the 3 official language versions formed the database that allowed an analysis of those differences to proceed. Although the analysis of the differences between the 3 versions was conducted and written up by me – in English – I would not have been able to make sense of the data without their extensive input and their willingness to give up

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The help and assistance of all of the above were invaluable in the completion of this thesis; responsibility for any inaccuracies in the thesis, of course, remains with me.

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too many to name and I fear that, in naming many and forgetting anyone, I may cause hurt feelings. So please, accept my sincere thanks, all of you who have in any way contributed to the long haul that completion of this thesis has been.

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ABBREVIATIONS

BMA	British Medical Association
BMJ	British Medical Journal
CIOMS	Council for the International Organisation of Medical Sciences
DoH	Declaration of Helsinki
MEC	Medical Ethics Committee (of the WMA)
NMA	National Medical Association
NoC29	Note of Clarification to Paragraph 29
NoC30	Note of Clarification to Paragraph 30
WMA	World Medical Association

For stylistic purposes, the full names of these may sometimes be used. Any other abbreviations to be used in the text will be introduced in the paragraph used [e.g., British Medical Association (BMA)].

Various revisions will be referred to as follows:

1st (Tokyo, 1975) revision or simply Tokyo (1975) revision or even 1st revision (where context renders meaning evident)
2nd (Venice, 1983) revision or Venice (1983) revision or 2nd revision
3rd (Hong Kong, 1989) revision or Hong Kong (1989) revision or 3rd revision
4th (Somerset West, 1996) revision or Somerset West (1996) revision or 4th revision
5th (Edinburgh, 2000) revision or Edinburgh (2000) revision or 5th revision
6th (Seoul, 2008) revision or Seoul (2008) revision or 6th revision

ABSTRACT

The Declaration of Helsinki (DoH) is a set of normative ethical guidelines developed by the World Medical Association (WMA) for doctors participating in medical research. Arguably the best known and most authoritative of such ethical guidelines, the DoH has roots in the Nuremberg Code (1947). First adopted in 1964, the DoH, by 2000, had been revised 5 times. The 5th (Edinburgh, 2000) revision gave rise to great controversy evidenced by the unprecedented step of the WMA issuing Notes of Clarification to the 2 most controversial paragraphs. This thesis considers in detail the text of the 5th (Edinburgh, 2000) revision. Beginning with a review of the historical evolution of the text, there follows description of the controversial issues, discussion of why controversy ensued and what may be the future of the text. Then a detailed paragraph-by-paragraph analysis details exactly what changed in the text and identifies the most significant changes. Seven major areas of change to the text were identified: use of placebos in research, post-research duty of care to individual participants, duties to ensure reasonable likelihood of benefit to communities involved in research, ethical issues related to publication, the addition of observational research to the scope of the document, the DoH's enhanced statement of its own authority, an enhanced duty to conduct research as well as an 8th major change, a logical re-structuring of the document removing the category of "Non-Therapeutic Research". Based on observation of

WMA meetings and archival research a "behind the scenes" analysis is undertaken – asking how the most controversial paragraphs came to take their form in the 5th revision and considering what lessons may be learned from the drafting process itself. Further, the DoH exists in three official languages (English, French and Spanish) and important differences were discovered. There follows a comparison of the three official language versions – investigating concerns as to how differences may lead to uneven application of the DoH but also asking how the differences may help in understanding the controversial paragraphs.

This detailed analysis of the text of the 5th revision leads to the central thesis question: "Is the DoH providing adequate guidance as a set of normative ethical standards across the broad spectrum of those involved in the global medical research endeavour as evidenced by reasonable coherence of their interpretations of the DoH?" Or, on the other hand, are the interpretations so diverse that the DoH cannot be considered a source of clear guidance. Or, put another way and incorporating the symbolism inherent in the title of this thesis: "Does the DoH function adequately to map the 'landscape of medical research'"? Semi-structured interviews were constructed based on the 8 major changes identified above and 57 experts drawn from 3 major categories: the "Authors" (15 people involved in the drafting process); the "Medical Researchers" (21 interviewees directly involved in conduct or application of medical research) and the "Expert Commentators" (21 with expertise in other aspects of drafting documents such as the DoH but not

directly involved in either of the above) were interviewed. The interpretation process as illustrated in the transcript of the interviews is analysed with a view to determining whether the 5th revision has been effective in achieving a workable agreement among interpretations. Analysis of the results showed the DoH to be variously successful in depicting the landscape of medical research between and amongthe above three groups of interviewees.

During the course of this study a further revision of the DoH took place in 2008 and the WMA invited a submission from this author as part of the consultation process. This response is presented and some discussion of the possible influence of this ensues.

Finally the summary and conclusions ask what has changed in the 2008 text in the critical parts of the DoH identified above before summing up and considering possible future trajectories for this globally important document addressing the ethical conduct of medical research.

The 5th Revision of the Declaration of Helsinki and the Ethical Landscape of Medical Research

1. INTRODUCTION

CHAPTER 1: INTRODUCTION

The World Medical Association's Declaration of Helsinki was first adopted in 1964. Its historical roots lie in the Nuremberg Code (1947 – see Appendix 1). This code was developed in conjunction with the trials of the Nazi doctors accused of involvement in horrific medical experiments in concentration camps in the 1930s and 1940s [Schmidt, 2007]. In its 40+ -year lifetime the Declaration has been revised 6 times and has risen to a position of prominence as a guiding statement of ethical principles for doctors involved in medical research. The DoH has been described as the "cornerstone" document pertaining to medical research ethics [Crawley, 2003] and as "the most widely recognised source of ethical guidance for biomedical research" [Macklin, 2003]. The 5th revision, however, resulted in considerable controversy, particularly in the area of the ethical requirements surrounding placebo-controlled trials and the question of responsibilities to research participants at the end of a study. There is a great deal at stake with respect to the status of the DoH as a global instrument articulating normative ethical guidelines for medical research. Of even greater concern, a decline in influence of the DoH will be one less avenue available to which doctors and others involved in medical research can appeal should they have ethical concerns about particular research endeavours.

On July 18, 1964 the British Medical Journal announced the birth of the DoH with the following words: "A draft code of ethics on human experimentation was published in the British Medical Journal of 27 October 1962. ... A revised version was accepted as the final draft at the meeting of the World Medical Association in Helsinki in June 1964. ... *It is to be known as the Declaration of Helsinki*" [Anonymous BMJ article, 1964] (emphasis mine). Attached to this inconspicuous announcement was the just over 700 words of the text of the original DoH heavily influenced by the text of the Nuremberg Code (1947).

The now "archaic" text of the 1964 version is illustrated by the use of phrases such as "fully qualified medical man", a phrase that would be removed in the 1st (Tokyo, 1975) revision. That 1st revision was an even greater revision, in terms of the proportion of the text that was revised or added, than the 5th (Edinburgh, 2000) revision. The text for the first time mentions the additional protection for research subjects that proposed research be reviewed by an independent committee although at this stage the review only stipulates that it is for "consideration, comment and guidance".

The minor revisions of 1983, 1989 and 1996 made little change to the text so it is effectively the 1975 version that held sway as the primary international statement of medical research ethics for 25 years. This occurred despite the internal upheavals

of the WMA itself, and the formation of the breakaway "Toronto Group" in the 1980s. The "Toronto Group" was a group of nations leaving the WMA structure in protest at the organisation's refusal to condemn the apartheid South African government's treatment of Steve Biko. With the end of apartheid and a formal apology, all nations had re-joined by 1992. None of this, however, seemed to dent the status of the DoH as an international ethical guideline for medical research ethics [Richards, 1994].

Then came news of the existence of the now "infamous" materno-fetal HIV trials in the 1990s [Angell, 1997; Macklin 2004; Williams, 2004] and the wording of the DoH, arguably sitting in the background suddenly came to the fore. The 1996 version, current at the time, stated: "The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists". Effective treatment was known to exist and a placebo-controlled trial was being conducted in clear violation of this paragraph of the DoH. The text of the DoH was being used as evidence of unethical conduct and suddenly the DoH caught the attention of all interested in global medical research ethics. Were the trials justified by being conducted in parts of the world where no treatment was available and so a placebo-arm deprived no-one of something they would have otherwise had? Therein lay the key question as to whether a double-standard was permissible across different parts

of the world [Macklin, 2004]. However, the DoH would seem to stand squarely against such a position.

It is not the purpose of this thesis to investigate the conduct of those trials. Rather, the focus is the text of the DoH. These episodes are mentioned because they were instrumental in driving demand for a review of the text of the DoH. Williams (2004) reviews the relevant history but in brief: a 1997 proposal by the American Medical Association was rejected by the WMA and Dr Robert Levine of Yale University was asked to convene a Working Group to consider the text. The proposal of this Working Group was also not accepted and the group colloquially known as the "3 Wise Women" (Drs Katy Myllymäki of Finland, Judith Kazimirski of Canada, and Nancy Dickey of the United States) set to work. A good deal of the detail of the rest of the story of the 5th (Edinburgh, 2000) revision is contained in the pages to follow.

In October 2000, the WMA Assembly convened in Edinburgh. Following the Council Meetings (see Chapter 4 for details), the main Assembly was opened by the Rt. Hon. Donald Dewar, First Minister for Scotland. This is an episode particularly poignant for recent Scottish history as within a few days, Scotland's first First Minister of the new parliament died suddenly of a brain haemorrhage (on October 11, 2000 [Anonymous BBC News Report, 2000]). This was clearly one of his last speeches to an international assembly. By the time of his tragic and sudden

death, of course, the WMA had adopted the 5th revision of the DoH, the Assembly had closed, the new version had been posted on the WMA website and so began the controversy surrounding the new text of the DoH and the possible impact it would have on the conduct of medical research around the globe.

The extent of the controversy is evident in the literature that will be presented in the ensuing chapters. However, further evidence of how deeply the text of the DoH had stirred up a response was in the WMA's response. The Annual Assembly of the WMA in 2001 had to be cancelled because of the events of September 11, 2001. However, a Council meeting was held instead and the text of a Note of Clarification to Paragraph 29 (relating to placebo use) was drafted and published on the website. It had to wait until the 2002 Annual Assembly in Washington for formal adoption as part of the DoH. However, this was quite unprecedented in the then 38-year history of the DoH. Immediately following this began the debate about a Note of Clarification to Paragraph 30 (regarding post-trial duty of care). That debate lasted for 2 years until the adoption at the Annual Assembly in Tokyo of that 2nd Note of Clarification. These Notes of Clarification reflect again the depth of controversy engendered.

Thus, it is hoped that the value of an in-depth analysis of the text of the 5th (Edinburgh, 2000) revision of the DoH can now be seen. The DoH is both influenced by and influences global thinking about the ethical dimension of

medical research. It is hoped that the following chapters can shed further light on this. Indeed, it is hoped that by shining such light across the changing landscape of medical research as the change is occurring and also on one of the most important maps that we have of the ethical dimensions of that landscape (the DoH), we can achieve a better understanding of both; and through that understanding facilitate a more ethically sensitive medical research endeavour.

1.1 Thesis Statement

This thesis began with two overarching purposes and events with respect to the DoH have necessitated a third:

1. An in-depth analysis of the text of the 5th Revision asking essentially "what changed?" (and as a corollary "what did not change?" as this was also controversial as will be seen); "what does it say now?" (in all 3 language versions); and "why has it been so controversial in comparison with earlier revisions of the Declaration of Helsinki?"

2. The 2nd over-arching purposes is to ask the question: "Is the DoH acting to bring together ethical perspectives across a broad spectrum of experts involved in medical research and the ethics thereof?" What is meant by this question? It is useful here to consider the Declaration of Helsinki symbolically in terms of a map. An accurate contour-map, drawn to an appropriate scale and read by those skilled in map-reading could be expected to lead similar descriptions of the landscape were

those skilled map-readers to be asked to describe what is depicted by the map. Likewise, do the various interpretations of the Declaration of Helsinki lead to a similar outcome with respect to the description of the "landscape" of medical research ethics when various experts from a variety of relevant perspectives are asked to "read the map"? The 2nd part of this thesis will consider this question with respect to the paragraphs of the DoH that appear to present the greatest interpretive difficulty.

3. Finally, time moves on, and during the course of this work a 6th revision of the Declaration of Helsinki was adopted by the World Medical Association's Annual Assembly in Seoul in 2008. This author (and supervisors) were asked, prior to the revision, for input into the revision process and this is documented in the 3rd part of this thesis.

1.2 Thesis Structure

The basic structure of the thesis is here overviewed:

Chapter 1: Introduction

Chapter 2: This is a review chapter – in effect a more extended introduction and literature review. It focuses on the background to the DoH, the evolution of the text over its various revisions, and an analysis of the controversial changes..

Chapter 3: No analysis of a document can be comprehensive without at some point undertaking a painstaking analysis of the text of the entire document. This chapter represents the detailed, paragraph-by-paragraph, analysis of the 5th (Edinburgh, 2000) revision of the DoH. Throughout this survey of the entire document the question is asked, "what changed in the 5th revision?", and a comprehensive database of such changes is thus generated. The information gleaned from such an analysis forms the critical basis for the decisions as to which paragraphs on which to focus in the semi-structured interviews (the methodology and results of which are described in chapter 6).

Chapter 4: The "organisational and voting structures of the WMA" have been described as "Byzantine" [Schmidt & Frewer, 2007]. This is perhaps unfair as any complex organization, let alone one dealing with organisations representing over 80 countries [WMA, *Members List, 2011*], is likely to have complex committee and decision-making structures. However, few have had the opportunity to observe how the WMA actually drafts and adopts a document such as the DoH. This chapter, through observing meetings and archival research goes "behind the scenes", analyzing in detail the processes of the World Medical Association, and how the most controversial changes to the DoH came about. Lessons can be learned from the process of revising the DoH that perhaps explain some of the controversial

response of those involved in various facets of medical research to the changes in the 5th (Edinburgh, 2000) revision.

Chapter 5: The DoH is a document that attempts to influence the ethics of medical research around the globe. It will thus eventually be translated into a multiplicity of languages. However, there are three official language versions in which the WMA operates: English, French and Spanish. Therefore, there are three official versions of the Declaration of Helsinki and none have pre-eminence over the other. This document thus "exists simultaneously" in three languages and there are differences between the versions. Are these differences important? Many are stylistic only but some may have important implications for the ethical conduct of research. This chapter focuses around a paper published by the author about the matter and delves further into the relevant literature relating to the Declaration of Helsinki.

Chapter 6: At the end of the above complex analysis of the text of the 5th (Edinburgh, 2000) revision of the DoH, what are arguably the 8 most important changes have been distilled. These are: (1) The control arm in clinical trial – in particular the use of placebos, and, where placebo is not used, the appropriate standard of control arm; (2) the post-research duty of care to research subjects; (3) the duty to communities or populations from which research subjects are drawn; (4) ethical issues related to publication of research; (5) the addition of observational research (research on "identifiable human material or identifiable data") to the

scope of the document; (6) the DoH's enhanced statement of its own authority; (7) an enhanced duty to conduct research according to 4 particular criteria; (8) a restructuring of the logic of the entire document removing the category of "Non-Therapeutic Research".

This chapter presents the results of a series of 57 semi-structured interviews of a variety of experts chosen on one of three bases: (1) **Authors** – those involved in the WMA's authorship process; (2) **Medical Researchers** - those directly involved in some element of the global medical research endeavour particularly with respect to drug development and drawn from a broad range of perspectives including the pharmaceutical industry, medical publishing, regulatory agencies, academic pharmacology and medicines evaluation; (3) **Expert Commentators** – those, who by virtue of their area of expertise, can be considered to have an important view regarding a document such as the DoH. Some have been involved in drafting other important international instruments such as the CIOMS guidelines. This category includes medical ethicists, philosophers, lawyers and medical historians among their academic disciplines. Of the 57 interviewees, 15 were classified as "**authors**", 21 as "**medical researchers**" and 21 as "**expert commentators**" according to the above descriptions and based on their primary reason for inclusion in the study.

This chapter is the section of the thesis addressing the 2nd of the three overarching purposes of the thesis. There is a detailed analysis of the way that these various experts are interpreting the text of the most significant changes in the DoH. The chapter asks whether, across this broad spectrum of interested "experts", there is evidence that the Declaration of Helsinki is indeed being interpreted in sufficiently similar ways that the DoH can be seen as a reliable source of ethical guidance in the conduct of medical research.

Chapter 7: This is the work done by this author in response to a request of the World Medical Association to submit suggestions regarding the 6th Revision of the Declaration of Helsinki. It represents a detailed analysis of the proposed paragraphs of the new revision incorporating where possible the work of Chapters 2-6. The full effects of this submission are impossible to judge. However, a reading of the submission and the resultant 6th revision suggest that at least some of the submitted material has influenced the text of the 6th (Seoul, 2008) revision of the DoH.

Chapter 8: Summary and conclusions. How has the 6th Revision addressed the textual concerns raised in the above chapters? How might research into this important document and its influence on medical research be taken forward? What might be the possible future of the DoH? These are all addressed in the concluding portion of this thesis.

Material from Chapters 2 and 4 has been published published as jointly authored works and from Chapter 5 as a book chapter. All of the text presented in this thesis was written by the author of this thesis and the contributions made by those who co-authored the work is described in the "Acknowledgements" above. Chapter 7 was written by this author (except for the approximately 800 words contributed by Professor Boyd – which are clearly delineated in the chapter). It is presented as a jointly authored work because this chapter formed the response to a request from the World Medical Association for our views regarding the 6th (Seoul, 2008) revision of the DoH. The request was made to myself and to my two supervisors so, as a matter of courtesy, the response was framed as being from the 3 of us. My supervisors provided advice on the content according to the normal manner of the PhD supervision process and agreed to their names being added to the final submission made to the WMA. By leaving in situ the portion of text written by Professor Boyd and by preserving the use of the 1st person plural pronoun "we", readers of Chapter 7 can see the actual text of the submission as it was sent to the WMA. This may be important for those wanting to reflect further on how this material may have influenced the 6th (Seoul, 2008) revision.

2. THE EVOLUTION OF THE TEXT AND THE CHALLENGES OF THE 5th (EDINBURGH, 2000) REVISION

CHAPTER 2: THE EVOLUTION OF THE TEXT AND THE CHALLENGES OF THE 5th (EDINBURGH, 2000) REVISION

2.1 Introduction

The Declaration of Helsinki (DoH) is, indisputably, a remarkable document. The 5th (Edinburgh, 2000) revision contains fewer than 2000 words. In these relatively few words, the World Medical Association (WMA) spells out a set of ethical guidelines for physicians and other participants in medical research. At the Scientific Session held in association with the World Medical Association's annual assembly of October 2003, various independent experts on research ethics confirmed the central role of this document. At this meeting the DoH was described as the "cornerstone" document pertaining to medical research ethics [Crawley, 2003] and as "the most widely recognised source of ethical guidance for biomedical research" [Macklin, 2003]. Yet the DoH's guideline statements are not without controversy; and even more so since the most recent revision at the 16th Annual Assembly of the WMA in Edinburgh in October 2000.

In this chapter I review the past and outline the present form of the text of the DoH. The major changes in the Edinburgh (2000) revision are outlined along with some of the controversies to which they have given rise. Throughout this chapter I focus

on the text that emerges at each stage of the process. The process leading to each revision is documented by the WMA at its own website [WMA, *Chapter 4,* 2003] and Chapter 4 of this thesis reviews in detail the process involved in finalising the text of what became Paragraphs 19, 29 and 30. I aim, through this chapter to familiarise the reader with the current content of the DoH and an historical understanding of how the Declaration has changed with each revision and so to set the stage for the more detailed analysis of the DoH that follows in subsequent chapters.

Since, for the most part, researchers and others seeking to implement the guiding principles of the DoH have not attended WMA meetings and have no easy means of access to the 'intent' behind the text as it emerges, my emphasis is on the text which emerges rather than the debate which leads to the text. In this situation, however, the WMA is able to monitor both changing events in medical research and readers' response to and interpretation of the DoH and the Declaration can be modified accordingly. This was explicitly stated in the 1975 version of the DoH: "[the recommendations] should be kept under review in the future" (see Appendix 2). Although the Edinburgh (2000) amendment saw this statement removed, in this sense, at least, the DoH can be conceived of as a 'living document'.

2.2 Declaration of Helsinki: Past

The British Medical Journal announced the emergence of the DoH in its July 18, 1964 edition with the following words: "A draft code of ethics on human experimentation was published in the British Medical Journal of 27 October 1962. ... A revised version was accepted as the final draft at the meeting of the World Medical Association in Helsinki in June 1964. ... *It is to be known as the Declaration of Helsinki*" [Anonymous, 1964] (emphasis mine). Attached to this inconspicuous announcement was the just over 700 words of the text of the original DoH. There seemed little indication at the time of how important this document would become in the context of research ethics.

One of the darkest episodes in the history of medical research – the horrific experiments carried out by doctors on concentration camp victims in Nazi Germany – was exposed at the Nuremberg trials of 1947. Emerging from the Nuremberg trials was a code of ethics setting out "standards to which physicians must conform when carrying out experiments on human subjects". The original DoH is seen as having its roots in the Nuremberg Code (see Appendix 1). Fluss identifies 12 markers of ethical research within the Nuremberg Code [Fluss, 1999]. He points out that, of these, 10 markers appear in the original DoH and two markers are abandoned. The Nuremberg requirement that "The voluntary consent of the human subject is absolutely essential" is changed and the DoH allowed consent to be given

by the "legal guardian" in cases of "legal incapacity". The other abandoned "marker" was the statement "During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible". This somewhat confusing statement was eliminated in the original DoH and appears to be covered most closely by the sentence: "The investigator or the investigating team should discontinue the research if in his or their judgment it may, if continued, be harmful to the individual". This is, of course, in addition to the subject or subject's legal guardian's freedom to withdraw consent at any time [WMA, 1964].

The original DoH also states "In the field of clinical research a fundamental distinction must be recognised between clinical research in which the aim is essentially therapeutic for a patient, and clinical research the essential object of which is purely scientific and without therapeutic value to the person subjected to the research" [WMA, 1964]. This led to the fundamental structure of the document. The paragraphs of the original and the first 4 revisions of the DoH are grouped under the headings "Introductory statements", "I. Basic principles", "II. Clinical research combined with professional care" and "III. Non-therapeutic clinical research". This structure persisted until the Edinburgh (2000) revision when it was substantially revised and I return to this issue under "Declaration of Helsinki: Present".

2.2.1 First Revision: Tokyo (1975)

The first revision to the DoH was adopted by the WMA at its 29th annual assembly in Tokyo (1975). This document was drafted by three Scandinavian professors of medicine. Despite the fact that none of them was working in their first language, the version of the Declaration they produced was adopted by the assembly virtually unchanged – a remarkable achievement [Flanagan, 1997].

The document was extensively revised. Arguably the single most important addition in terms of the ensuing conduct of medical research was the requirement that independent committees review research protocols. Another major development was a significant elaboration of the requirements for informed consent. These requirements were also moved to the section entitled "Basic Principles" (see Appendix 2; Paragraphs I.9-I.11). Additional considerations regarding informed consent are presented in the section pertaining to "Medical Research Combined with Clinical Care". These changes coincided with a simplification of the consent requirements for "Non-therapeutic" research wherein it is now simply stated "The subjects should be volunteers" (Paragraph III.2). Since the elaborated principles in the section "Basic Principles" apply both to the "Clinical" and to the "Non-therapeutic" category of research there was no net loss of protection for subjects.

Table 2.1 outlines summary statements of the most important changes which took place in the 1975 revision. Appendix 2 gives the full text of the 1975 DoH. In addition to the major changes in content, there was a revision of the overtly sexist language in the 1964 version. The phrase "fully qualified medical man" was changed to "medically qualified person" (see Paragraph I.3) and the use of the pronoun "his" in reference to "doctor" in the 1964 version was changed to "his or her".

Table 2.1: Key changes in the Tokyo (1975) revision of the Declaration of Helsinki.

Introduction:

3rd, 4th and 5th Paragraphs:	Nature and purpose of medical research
6th Paragraph:	Respect for environment and for animals used in research
7th Paragraph:	Keep Declaration under review

Basic Principles:

I.2	Independent committee review of research protocols
I.5	Interests of human subject must prevail over interests of science and society
I.8	Obligations regarding accuracy in publishing
I.9-I.11	Enhanced requirements for informed consent
I.12	Protocol must declare that requirements of Declaration of Helsinki adhered to

Medical Research Combined With Professional Care (Clinical Research)

II.2	Best current therapy should be comparator arm
II.3	Assurance of access to best proven methods
II.4	Refusal of research participation not to affect doctor-patient relationship
II.5	When doctor considers it is essential not to obtain informed consent*

Non-therapeutic Biomedical Research Involving Human Subjects (Non-clinical biomedical research)

III.2	Less detail regarding consent (most of detail moved to Basic Principles section)
III.4	Wellbeing of subject takes precedence over Interests of science and society (see I.5)

* This is the only paragraph from the 1975 (and subsequent minor revisions) completely removed at the Edinburgh (2000) revision

(N.B. These are listed under the numbering system of the paragraphs in the Declaration with the exception of the "Introduction" section, which is not numbered)

The revision which took place in 1975 was even more extensive, as a proportion of the starting document, than the Edinburgh (2000) revision. Almost nothing was removed from the 1964 version and much was added. The result was an almost doubling in the length of the document. Given the relatively minor revisions of 1983, 1989 and 1996 (see below), it is effectively the 1975 version of the DoH which became the guiding document for the ethics of research involving human subjects for a quarter of a century.

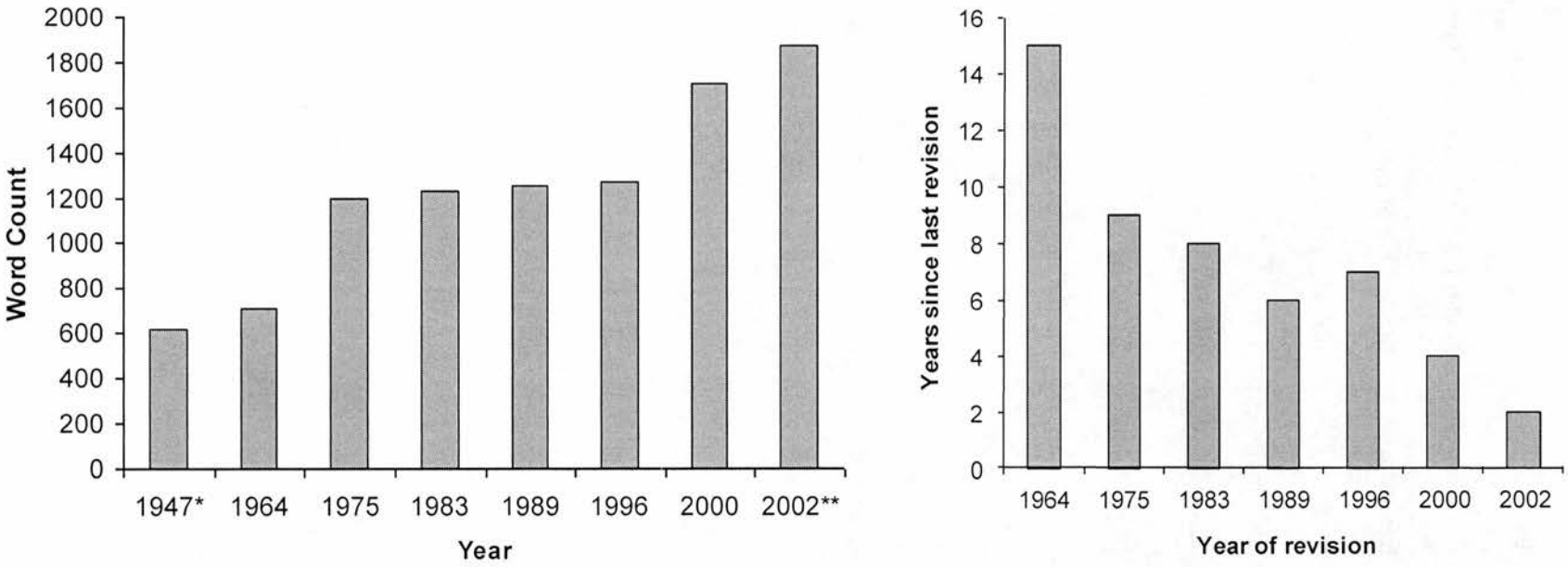
2.2.2 Second Revision: Venice (1983)

Given the extensive nature of the revision in 1975, it could be argued that the very minor changes of 1983 hardly warrant the term revision. However, it is the practice of the WMA in respect of the DoH to list all amendments in the preamble to the Declaration with no indication whether the amendment was major or minor. This practice has only been varied with the addition of the Note of Clarification to Paragraph 29 in 2002 which is mentioned in the preamble (see Appendix 3) but not described as a revision since the text of the actual paragraphs of the Declaration did not change.

In 1983 there were 4 fairly minor changes to the text of the DoH [WMA, 1983]: The word "doctor(s)" was changed to "physician(s)" in the 16 instances where the word occurred in the 1975 version. In the "Introduction", the quotation from the Introduction from the International Code of Medical Ethics changed slightly as the wording of this code had changed. Also in the "Introduction", the Latin phrase *a forteriori* was changed to "especially" in the statement "In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research". Finally, in the "Basic Principles" section, the requirement that where a minor is able to give "a consent" that such consent should be sought was added to Paragraph I.11 dealing with situations of legal incapacity for consent.

Since nothing was removed from the document these minor revisions led to an increase in the length of the document which now comprised just over 1200 words (see figure 1).

Figure 1: Word count for each revision of Declaration of Helsinki and years since last revision



*Nuremberg Code **Includes Note of Clarification

2.2.3 Third Revision: Hong Kong (1989)

This revision requires a fairly careful reading to see where any difference at all occurs. The only change in wording which occurs is in Paragraph I.2 under the section "Basic Principles". Previously the Declaration required that experimental protocols "should be transmitted to a specially appointed independent committee for consideration, comment and guidance". This was considerably elaborated in 1989. Protocols were now to be "transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed" [WMA, 1989].

Given the requirement, as already stipulated in the introduction, that "physicians are not relieved [by the DoH] from criminal, civil and ethical responsibilities under the laws of their own countries" it has to be questioned whether the additional requirements in Paragraph I.2 are unnecessarily repetitive. It should be acknowledged that such repetition is not without precedent. From the Tokyo (1975) revision reference to national legislation is made in the paragraphs referring to

informed consent. It could be argued that the use of repetition stresses the need for reference to national legislation in the instances in which it occurs.

Overall, the effect of the minor revision in 1989 added 29 words to the length of the DoH (Figure 1).

2.2.4 Fourth Revision: Somerset West, South Africa (1996)

As in 1983 and 1989, the actual changes to the text were minimal. However, the nature of the small textual change provided a seed out of which grew a much larger debate. In 1996, at the 48th General Assembly [WMA, 1996], the WMA adopted the following addition (shown in italics) to Paragraph II.3 in the section pertaining to "Medical Research Combined with Clinical Care (Clinical Research)":

> "II.3 In any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method. *This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists*". [Italics mine]

This occurred in the context of rising disquiet about the use of placebo controls in

studies of materno-fetal HIV transmission. It is the first time the DoH makes reference to any specific type of research methodology, i.e. the placebo-controlled trial. A careful reading of Paragraph II.3 without the addition would appear to have the same requirement on researchers but for the first time the DoH refers specifically to placebo. It is the addition of this specific requirement that meant that the Food and Drug Administration of the United States chose to continue to refer to the 1989 version of the DoH in its regulations [Temple, 2003]. This brings us neatly to the present version of the DoH with its attendant controversies.

2.3 The Declaration of Helsinki: Present

I do not outline every detail of the textual changes since only 3 of the 32 paragraphs are completely unchanged while 8 are completely new [Nicholson, 2000]. Also, since the focus in this chapter is on a review of the text of the Declaration, the events surrounding the eventual Edinburgh (2000) amendment are not reviewed here. They are described in detail by Human and Fluss in documents readily accessed at the WMA website [Human & Fluss, 2003; WMA, *Chapter 4,* 2003]. Additionally, In Chapter 4 of this thesis I present archival research that considers in detail how the text of what eventually became paragraphs 19, 29 and 30 developed through a series of WMA Council Meetings.

However, for the present chapter the focus remains on the text of the DoH that emerged with each revision – up to an including the 5th (Edinburgh, 2000) revision. I single out for comment the revised structure of the document, the most controversial of the new Paragraphs – 19, 29 and 30 – and four other Paragraphs (1, 6, 9, 27) which, although they have not yet given rise to significant debate in the literature, are striking changes in the way the document addresses aspects of medical research ethics. The text of the DoH, Edinburgh (2000) revision is appended to this thesis (Appendix 3).

2.3.1 A re-structured document

In all versions up to the 2000 revision the following structure applied to the document: there was an Introduction (where the paragraphs were not numbered) followed by numbered paragraphs under the headings of "Basic Principles", "Medical Research Combined with Professional Care (Clinical Research)" and "Non-therapeutic Biomedical Research Involving Human Subjects (Non-clinical Biomedical Research)" (See Appendix 2; the 1975 version of DoH illustrates this structure).

The 2000 version of the DoH is completely re-structured. There is now a section headed "Introduction" comprising Paragraphs 1 to 9 which sets out the scope of the document and some of the underlying principles. Although many of the statements in

the "Introduction" were present in previous versions of the Declaration, they have been re-ordered to present a more logical sequence of reasoning. Arguably one of the most important statements is the requirement in Paragraph 5 that "In medical research on human subjects, considerations related to the well-being of the human subject should take preference over the interests of science and society". By the end of the introduction the document has very clearly set up the dilemma that gives rise to the need for clear thinking about research ethics. On the one hand, it would be unethical not to challenge current methods in medical practice (Paragraph 6) through research. On the other hand, it is wrong to simply use people as a means to an end (Paragraph 5), particularly vulnerable people (Paragraph 8). Having described this ethical tension in the "Introduction" the DoH then seeks in the next 2 sections to articulate the guiding principles for deciding what research meets the ethical standards required and what does not.

After the introduction, there follow Paragraphs 10 to 27 under the all-encompassing heading "Basic Principles for All Medical Research". Finally, there are an additional 5 Paragraphs (28 to 32) under the heading "Additional Principles for Medical Research Combined with Medical Care". In this section are found the controversial Paragraphs 29 and 30.

This is a major logical re-framing of how the DoH categorises different types of research involving human subjects. The pre-2000 versions of the Declaration

effectively dichotomised research into therapeutic (potentially benefiting the subject directly) and non-therapeutic (no direct benefit to subject). In the Edinburgh (2000) revision the new category of "Medical Research Combined with Medical Care" is recognised as a subset of "all medical research involving human subjects".

There is no longer any specific section dealing with "Non-therapeutic" research, which is often viewed as synonymous with "healthy volunteer" research. There is specific reference to "healthy volunteers" in 3 paragraphs of the Edinburgh (2000) revision. Paragraph 16 explicitly states that participation of healthy volunteers as research subjects is permissible. Were this not stated, then a certain way of interpreting Paragraph 19 may lead to the conclusion that such research was now proscribed. In Paragraph 18 healthy volunteers are identified as a group where the importance of prior weighing of the importance of research against its risks and burdens is especially important. Finally, Paragraph 8 in the "Introduction" lists "those who will not benefit personally from the research" among those groups that are vulnerable and in need of special protection.

This revision of how research is categorised has been strongly supported by Levine [Levine, 2000] as removing a previously illogical distinction. It must be of concern, however, that there is no longer a section of the DoH dealing with research where there is no potential benefit to the participants. Such groups do present some

differences in methods of recruitment and such participants are often paid for their participation in research. These issues need further consideration and debate.

2.3.2 Paragraph 29

The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists .

As already mentioned, the 1996 version of the DoH is the first version of the DoH to mention specifically the use of placebo in trials. Paragraph II.2 from the 1996 stated "The potential benefits, hazards and discomfort of a new method should be weighed against the best current diagnostic and therapeutic methods". This has been changed to the wording seen in the first sentence of Paragraph 29 (above). The sentence which then followed in the 1996 version (and which formed the first sentence of Paragraph II.3) stated "In any medical study, every patient – including those of a control group, if any – must be assured of the best proven diagnostic and therapeutic method" has been eliminated. Finally, in the 2000 revision very little is changed in the actual sentence referring to placebo which is the 2nd sentence in Paragraph 29 (above); the words "inert placebo" from the 1996 version are changed to "placebo, or

no treatment". In a careful reading of the two versions, however, it appears that very little has changed in the overall ethical guidance with respect to placebo use. Therefore, what is surprising is that the outcry following the 2000 revision far exceeded the response to the 1996 revision.

The overall effect of Paragraph 29 would seem to rule out use of placebo wherever proven treatment exists. As mentioned, this raised such a cry of protest that the WMA took the unprecedented step of issuing, in 2001, a Note of Clarification to Paragraph 29 (see footnote). The Note of Clarification was formally adopted as part of the DoH in 2002 although the WMA has not described this as a "revision" since the actual text has not been modified – only "clarified"!

However, the Note of Clarification certainly seems to modify the requirements and represents the first occasion where the WMA have issued explanatory text indicating the intent behind a specific paragraph. One of the best summaries with respect to placebo use in trials is that of Emanuel and Miller [Emanuel & Miller, 2001] who define 3 broad positions: placebo orthodoxy, active-control orthodoxy and the "middle ground" (see Table 2.2 for definitions). It would appear that the Note of Clarification moves the stance of the DoH from what appears to be active-control orthodoxy towards the "middle ground". The debate in the literature over the ethics of placebo controls has raged for at least the past decade between the proponents of "active-control orthodoxy" such as Rothman, Michels and Weijer [Rothman &

Michel, 1994; Weijer *et al.*, 1997] and those supporting "placebo orthodoxy" such as Levine [Levine, 1999] and Temple [Temple & Ellenberg, 2000].

Table 2.2: Emanuel and Miller's 3 ethical positions with respect to placebo-controls [Emanuel & Miller, 2001];

Active-control orthodoxy	Middle ground	Placebo orthodoxy
"Whenever an effective intervention ... exists, it must be used in the control group ... placebo controls are inappropriate because the clinically relevant question is ... whether [a new drug] is better than standard treatment"	"when effective treatments exist, there must be compelling methodological reasons to conduct a placebo-controlled trial"	"Without a placebo group to ensure validity, the finding that there is no difference between the investigational and standard treatments can be misleading or uninterpretable"

The Note of Clarification lists two situations where placebo is acceptable: where there is a scientifically compelling reason or where the condition under study is minor and the subject at no increased risk of serious or irreversible harm. These two situations are linked by the word "or" which has been questioned by Macklin [Macklin, 2003]. She asserts that the connector should be "and" (i.e. both conditions must be fulfilled). The risk otherwise is that scientifically compelling reasons could be used to justify an increased risk of serious harm through use of placebo and this is argued to be inappropriate. This would be in line with the introductory principle of Paragraph 5 that "considerations related to the well-being of the subject should take

preference over the interests of science and society". The counter arguments are both that valuable research may be prevented [Neda, 2003] and that placebo-controlled trials often require a much smaller sample size and follow-up time and therefore expose fewer people to any risks inherent in the research [Emanuel & Miller, 2001].

A further issue with respect to Paragraph 29 has been the interpretation of the words "best current" as the standard of comparator arm. Does this mean best in existence or best available in a local context? The Note of Clarification does not address the issue. The UK Nuffield Council on Bioethics argues the issue extensively recognising that "The Declaration of Helsinki (2000) is the primary source of guidance on which the majority of other guidance draws" [Nuffield Council, 2002]. Their conclusion regarding the interpretation of "best proven" is that "the minimum standard of care that should be offered [in the control arm] is the best intervention available as part of the national public health system".

There is still considerable discussion around the circumstances in which placebo control is ethically acceptable. It seems clear that for some serious conditions where there is often "one chance" at cure – such as many forms of cancer – placebo-controls should be ruled out. At the other end of the scale, except for the most extreme adherents to "active-control orthodoxy" minor and self-limiting conditions seem to present little problem regarding placebo-use. It must be remembered that Paragraph 29 refers to "proven" treatment not "active" treatment. Just because a

pharmaceutical agent is shown to have pharmacological "activity" does not mean it has been properly "proven" to be superior to placebo. Indeed, such proof may never be forthcoming in some conditions where placebo response is either high or greatly variable. Symptoms of chronic stable angina, for example, can show a highly variable placebo response [Bienenfield *et al.,* 1996] and this condition is selected by Emanuel and Miller [Emanuel & Miller, 2001] as an example where a well-designed placebo-controlled trial should be satisfactory on ethical grounds provided patients are well-monitored for worsening symptoms, that appropriate 'rescue' or 'escape' medication is available, and participants are fully aware of their right to withdraw from the trial at any time.

In the middle of these extremes are many clinical scenarios where the issue of whether placebo-controlled research is acceptable or whether serious or irreversible harm is risked needs to be undertaken on a "disease-by-disease" basis. Among the conditions which have given rise to recent debate in this regard are hypertension [Weber, 1999], depression [Baldwin *et al.*, 2003], schizophrenia [Carpenter *et al.*, 2003] and post-menopausal osteoporosis [Delmas *et al.*, 2002]. Taking osteoporosis as one example, Brody and colleagues [Brody *et al.*, 2003] have pointed out that there are groups of patients in whom placebo-controlled trials clearly do not violate Paragraph 29. They specifically identify as suitable for placebo-controlled trials: "competent, well-informed patients [who] refuse approved therapies for sound reasons", situations where "there is a reasonable basis for substantial disagreement or

lack of consensus among professionals about whether approved treatments are better than placebos", or "subjects are refractory to known effective agents". It should be noted, however, that this approach may introduce biases.

A person consenting to participate in any blinded randomised controlled trial is effectively agreeing not to be given information that most individuals would want to receive; that is, to know what treatment they are receiving at any one time. This agreement not to know such information is not unique to trials using placebo-controls. Placebo-controls are not deemed unethical in and of themselves by Paragraph 29. What is called into question is the potential harm to research participants who may not receive otherwise available proven treatments during the course of a placebo-controlled study.

The issue of placebo-control, probably more than any other, highlights the need for delicate considerations to balance ethical tensions which often exist between research which seeks to obtain answers as efficiently as possible (and there is nothing inherently wrong with that) and the well-being of participants in research. The DoH, particularly in Paragraph 11 but also in other places throughout the document, affirms that unless research constitutes "good science" it is unethical. However, as already mentioned, Paragraph 5 places an ethical onus on the doctor never to sacrifice the interests of the individual in the interests of science and society. At the same time Paragraph 6, in particular, places an ethical duty on doctors to

undertake research. Taking any of the paragraphs to an extreme while ignoring the other paragraphs risks either endangering the well-being of participants or placing catastrophic barriers in the way of medical advance, which has the potential also to rebound to harm the individuals. The process of independent ethical review (Paragraph 13) and adequate informed consent (Paragraphs 22-26) must serve to protect the participants. Ethics committees are charged with deciding what kind of control group is ethically justified in individual protocols and ought to do so in full appreciation of the ethical tensions described above.

So, despite the adoption of the note of clarification, there is considerable work to be done on clarifying in what circumstances placebo-controlled studies are ethically acceptable. It would be useful to see evidence-based guidelines like those developed for mood disorders [Charney *et al.*, 2002] undertaken for a wide variety of conditions. This would greatly assist those designing research protocols and ethics committees in their required assessment of the risks and benefits (Paragraphs 16-19). Of course, such guidelines, to be useful, would need to be frequently updated to take into account medical advances.

Even after carefully thought out debate it is likely that there will still those who would wish to see the Declaration interpreted in a way that would place greater restriction on use of placebo [Michels & Rothman, 2003]. As Macklin cautions,

"Two paragraphs (29 and 30) ... remain controversial and would still be controversial if changed to meet criticisms" [Macklin, 2003].

2.3.3 Paragraph 30

At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

In the most recent edition of their highly successful textbook "The Principles of Biomedical Ethics", Beauchamp and Childress make the following observation: "Until the 1990s, the paradigm for ethical analysis focused on the risks and burdens of research... and on the need to protect potential and actual research subjects from harm, abuse, and exploitation. ... However, a paradigm shift occurred in the 1990s ... As a result, justice as *fair access to research* (participation in research and access to the results of research) became as important as protection from exploitation" [Beauchamp & Childress, 2009]. The most recent revision to the DoH, in particular Paragraph 30 but also reflected in Paragraph 19 (see below), would seem to bear this out. Nicholson asserts regarding Paragraph 30 that, "this is potentially the most far-reaching of all the changes to the Declaration" [Nicholson, 2000]. Concerns about the implications of Paragraph 30 have led to the WMA assembling a Workgroup to consider either an amendment to the paragraph or the addition of a note of

clarification. The report of the workgroup was presented to the Council meetings which preceded the most 2003 WMA General Assembly (held in Helsinki, 10-14 September, 2003) and it was decided that no amendment or clarification would be undertaken but that the workgroup's deliberations would be continued and consultations widened [Frankish, 2003]. Although this decision has drawn criticism [Anonymous Lancet editorial, 2003], I argue that it represents a "sensible and measured" approach to the situation [Carlson *et al.*, Lancet letter, 2003].

The debate centres on the issue of what happens to patients in a trial once the trial is over. Capron has characterised this as an example of the larger question "who owes what to whom and why?" [Capron, 2003] In contrast to Paragraph 29 where the critical question has been characterised as "are participants worse off in the trial than they were before the trial?" the question here is "are participants worse off after the trial than they were during the trial?" Those who see Paragraph 30 as imposing too great a burden on researchers emphasise the benefits which accrue to patients during a trial where there was no access to treatment beforehand and assert that nothing is lost (compared with the pre-trial situation) if, at the end of the trial, the status quo resumes and access is lost. In contrast, those supporting Paragraph 30 as it is emphasise the additional trauma and distress caused to patients who, after treatment for a duration of the trial, learn what is possible for them, only to be deprived of access when the status quo resumes post-trial. They argue that these patients are, indeed, worse off after the trial than they were before. There is no easy way towards

consensus on this and the WMA press release of September 24, 2003 - following the 2003 General Assembly - noted "sharp differences of opinion over how to protect human participants in medical research" [WMA,2003].

2.3.4 Other Major Changes in the Edinburgh (2000) Revision

Paragraphs 29 and 30 have given rise to the greatest controversy. It is arguable that they may have overshadowed debate about other paragraphs which have changed significantly. Space does not permit elaboration in detail of every change in the 2000 revision so I focus on significant changes introduced through Paragraphs 1, 6, 9, 19 and 27.

2.3.4.1 Paragraph 1

The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

Paragraph 1 outlines first of all the *raison d'être* of the DoH. Although the 1st sentence of what is now Paragraph 1 has not changed from the earlier versions, it has been moved to become the opening statement of the DoH. However, the second sentence of Paragraph 1 for the first time explicitly declares that the provisions of the DoH apply to identifiable human tissue and identifiable data.

Overall this paragraph has evoked little comment although Riis has raised two concerns [Riis, 2000]. Firstly, he considers that anonymised research should also be covered by the Declaration because of the possible harms associated with "group stigmatization". Secondly, he notes that there is "brief mention of 'human material' and 'data' without including statements applicable to epidemiological and large-scale genetics research". Certainly the explicit inclusion of identifiable material and data has taken place without any considerations of the possibility of different requirements for consent later in the document and this requires further consideration.

2.3.4.2 Paragraph 6

The primary purpose of medical research involving human subjects is to improve diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic,

diagnostic and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

The first sentence is not new to the 2000 revision of the DoH but the second sentence of Paragraph 6 is entirely new. This places a distinct ethical burden on physicians to challenge current methods through research. The choice of the 4 criteria by which existing methods are to be challenged (effectiveness, efficiency, accessibility and quality) is not further justified nor are the actual criteria defined. However, to any readers who would see documents such as the DoH as placing obstacles in the way of research, paragraphs such as this explicitly describe the very real ethical tension which exists and which is described as balancing "the protection of, and respect for, research patients and healthy volunteers with the necessary freedom of research to facilitate scientific progress as a public good" [Riis, 2000].

2.3.4.3 Paragraph 9

Research investigators should be aware of the ethical, legal and regulatory requirements for research on subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

To understand the sea-change which this statement represents we need to consider the paragraph which was included in all previous versions of the DoH: "It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries". From previously being seen as guidance which did not in any way supersede national regulations, the DoH has recast itself as a minimum set of international standards "binding" physicians worldwide.

It is perhaps very surprising that this paragraph has not given rise to greater controversy. The issue of the relationship between law and ethics is complex. However, it is noteworthy that in 2003 the WMA in 2003 issued their own statement on the matter: "In some cases the law mandates unethical conduct. The fact that a physician has complied with the law does not necessarily mean that the physician has acted ethically. When the law is in conflict with medical ethics, physicians should work to change the law. In circumstances of such conflict, ethical responsibilities supersede legal obligations" [WMA, *The law and medical ethics*, 2003]. This statement by the WMA applies broadly to the relationship between ethics and the law and is not limited to observation of the DoH. This statement of course gives no guidance to the physician in the situation where two ethical codes conflict. What should a physician of devout religious persuasion do, for example, if he or she believes that something in a secular ethical code is not in harmony with an ethical

code mandated by their faith? However, it is noteworthy that the Declaration of Helsinki itself has remained relatively free of any objections to it on the grounds that it clashes with other codes of ethics.

2.3.4.4 Paragraph 19

Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

This is another statement which projects the concerns of the DoH into the realm of social justice. There are those who argue that this is not an appropriate role for the DoH [Temple, 2003] and others who argue strongly that the DoH should play a major role in combating what have been described as "double standards" in the world of medical research [Macklin, 2003]. Issues surrounding this debate have been discussed under "Paragraph 30" above. Although not giving rise to the same degree of controversy as Paragraphs 29 and 30, there was sufficient debate about this paragraph to warrant calls for a Note of Clarification and documentation was prepared in this regard. It was, however, decided by the WMA Council in May, 2003 – at which I was an invited observer - not to proceed with a Note of Clarification to Paragraph 19.

2.3.4.5 Paragraph 27

Both authors and publishers have ethical obligations. In publication of the results of research the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affilitations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

Of the four sentences in this paragraph, the first and the last were present in previous versions and will not be discussed further. The 3rd sentence, requiring disclosure of potential conflicts of interests has parallels in Paragraphs 13 and 22. The overall result is that such potential conflicts must be disclosed to: (1) the committee undertaking independent review, (2) the patient when informed consent is sought and (3) in any research publication. Although the question of what constitutes a conflict of interest is not fully defined, there seems little objection to the inclusion of these requirements in the DoH.

The requirement to make negative results available also seems to raise little objection but should be recognised for the important advance that it is. As pointed out by Godlee, "Negative results are just as important to scientific understanding, if less exciting for researchers and editors, as positive studies". She asks "What has publication bias to do with ethics?" and answers "it gives only part of the picture and so distorts our views on what is the best treatment for patients" [Godlee, 2000].

There is now, within the DoH, a recognition that the publication bias which results from the propensity to publish "positive" results at the expense of "negative" results has the potential to harm patients and thus carries with it ethical obligations. Additionally, such a publication bias will distort the various analytic methods (such as cost-benefit analyses, cost-effectiveness analyses and so forth) that are used in determining how best to allocate health resources for the benefit of the population.

The difficulty however remains that publications seek to maintain their readership and that publishing positive results which may change the course of medical practice is widely perceived as more interesting than negative results which would tend to favour the status quo. It is possible that the internet may provide at least a partial solution and that negative results which would otherwise be unpublished may be made publicly accessible through the World Wide Web. The issue of electronic "open access publishing" has recently been debated [Delamothe & Smith, 2004]. One point of contention surrounds who pays for such publication and the recently launched Public Library of Science charges authors for publication.

Lacking completely in the debate in this recent article, however, is what effect these changes may have on the publication of negative results and avoidance of publication bias. Therefore, it still remains unclear whether the aspirations of Paragraph 27 will be achieved in practical terms.

2.3.4.6 Other changes

As pointed out above, the 2000 revision of the DoH left very few paragraphs unchanged. The changes not commented on in detail are listed in Table 2.3. The fact that I have not commented in detail is not an indication that the changes are considered unimportant but rather that their introduction seems to have caused little controversy.

Table 2.3: Other significant changes to the text of the Declaration of Helsinki in the 2000 revision (see appendix 3 for full text of Declaration of Helsinki);

Paragraph number:	Subject of the changes:
8 (new paragraph)	Research on people from vulnerable groups
13 (modified paragraph)	Ethics committees have the right to monitor research; disclosure of potential conflicts of interest to ethics committees
16 (modified paragraph)	Design of all studies to be publicly available
21 (modified paragraph)	Explicit mention of protection of confidentiality of information about the patient
22 (modified paragraph)	Provisions where consent cannot be obtained in writing
25 (modified paragraph)	"Consent" changed to "assent" with respect to research involving children
26 (new paragraph)	Provisions where consent from subject not possible
31 (modified paragraph)	Requirement to fully inform patient what aspects of their care relate to the research
32 (new paragraph)	Use of unproven techniques to save life or re-establish health should be made the object of research and the results recorded and published where appropriate

2.4 The Declaration of Helsinki: Status After 5th Revision

There is little doubt that the influence of the DoH remained a central guide to research practice. This is illustrated, at least in part, by the use of the Declaration by other important documents pertaining to research ethics [Idanpaan-Heikkila, 2003]. The Council for the International Organizations of Medical Sciences (CIOMS) guidelines on research ethics, for example, include the full DoH as an appendix and make extensive reference to the DoH in the text. In the longer term, it may be that the influence becomes "diluted" by the confusing proliferation of international guidelines, codes of practice and other instruments such as those recently developed by CIOMS, by the International Conference on Harmonisation (ICH) and by the Council of Europe. However, none of the above is really of the same genre of document as the DoH. Each is much lengthier, and attempts to cover questions of what to do in particular practical situations. The DoH, on the other hand, seeks to articulate a basic set of principles, to function as a code of ethics.

Therefore, it could be argued that the main influence of the DoH is not so much in answering specific questions about certain ethical protocols – although some of its paragraphs are certainly useful in that regard – but rather the DoH is part of the foundation on which these more detailed guidelines have been drafted.

There are a number of other trends which need consideration in terms of the future of the DoH. Probably the most important underlying question, however, is 'from where does the DoH draw its authority?' I consider four possible sources for this authority:

(i) The World Medical Association (WMA):

One possible answer is that it draws its authority from being a Declaration of the WMA. This is the largest global grouping of doctors and as such there may be legitimacy in the claim that it is an authoritative body for making statements about the collective views of the medical profession.

However, one historical observation would seem to undermine any argument that this explains the authority of the DoH. Arguably the Declaration's period of greatest acceptance as an authoritative document dates in the period from the late 1970's (after the 1975 amendment had been widely promulgated) to the mid-late 1990's when increasing calls for modification to the DoH began to be voiced. However, this was a period of considerable internal turmoil for the World Medical Association. In the 1980s, several countries (the so-called "Toronto Group") including the United Kingdom, withdrew from the WMA over ongoing objections to the refusal of the South African Medical Association to condemn apartheid. The events of history have allowed reconciliation of this rift and all of the breakaway countries had rejoined the WMA by 1995 [Richards, 1994].

This, I believe, calls into some question any conclusion that the DoH's authority rests solely, or even largely, on the nature of its "author". It may even be that as the WMA strengthens and enlarges that it may be more difficult to obtain consensus on documents such as the DoH and particularly on difficult Paragraphs such as 29 and 30.

(ii) The Declaration's Succinctness

Although there is also clear evidence of a trend toward the DoH becoming longer (see Figure 1) there is no doubt that the Declaration – still less than 2000 words in length – is one of the most succinct documents encapsulating the principles guiding research ethics in existence. It can be read from beginning to end in less than 10 minutes.

The increasing complexity of research issues means that it is hardly surprising that a lengthening has occurred. While the succinctness of a document may not contribute directly to a document's "authoritativeness" the question must be asked: How much has its succinctness helped to promulgate its widespread use? If this is a major basis of the DoH's influence then the increasing length of the document, and the use of "clarifications", must be a matter of great concern.

(iii) The Declaration's Long-standing Pre-eminence

There is an apparent tendency toward the DoH being changed more frequently (see figure 1). However, it must be recognised that only two of the revisions (1975 and 2000) were more than minor in nature. This means that the period between extensive revisions is 11 (from 1964-1975) and 25 (from 1975-2000) years respectively. Therefore the DoH, essentially in its 1975 form, had a quarter of a century to become embedded amongst those involved in medical research and this may contribute significantly to the position it has come to occupy. On the other hand, there is recognition of the need to update the document to recognise the changing world of biomedical research [Human & Fluss, 2003]. Finding the correct balance between the need to modernise the document and the necessity to allow the text to become familiar to those using it will be important to maintaining the status of DoH.

It should be pointed out that the delegates to the World Medical Assembly are well aware of these trends toward lengthening of the document and more frequent changes. The data shown in Figure 1 was presented during the President's opening address of the Scientific Session of the most recent World Medical Assembly in Helsinki [Myllymäki, 2003].

(iv) That the Declaration has Successfully Articulated More Broadly Accepted Principles;

Did the DoH achieve its authority because it accurately articulated deeply held and broadly-based ethical principles regarding the ethics of medical research? Almost like an ancient religious text, where commentaries debate the meaning of individual words, the DoH is the subject of almost a word-by-word analysis. Consider Article 29 where an enormous amount of ink has been spilled over the meaning of "best current". The Nuffield Council Document on "Research in Developing Countries" devotes an entire chapter to what is effectively a debate about the true interpretation of this phrase [Nuffield Council, 2002].

If this is the basis of the Declaration's authority then the relevant question is whether the Edinburgh (2000) revision represents a superior expression of these deeply and widely held values than its predecessors.

It is worth reflecting on the following: when controversies arise – such as those surrounding Paragraphs 29 and 30 – there really are only three broad reasons which may underline such controversies.

Firstly, if the wording of the document is at odds with the true underlying ethical principles then they must be better articulated, i.e. better 'word-smithing' is the way

forward. Secondly, it may be that there really is no universal consensus about the ethical issues at stake in which case some kind of 'agreement to differ' would be the only way to achieve a consensus document.

A third possible reason for a flurry of controversy over the wording needs to be considered. Has the document shone an uncomfortable light on practices which are questionable ethically? In this last regard, bioethicist H. Tristram Englehardt [Englehardt, 1996] speaks of the potential offensiveness of ethics. Aspects of his discussion could be paraphrased along these lines; to say someone is in the wrong *factually* has the potential to create a certain degree of offence but to say that someone is in the wrong *ethically* is to criticise at a much deeper level and may cause a much more profound level of offence. If the reason for the controversy over statements such as Paragraph 30 is that the text of the DoH has made parts of the research community feel very uncomfortable about the ethics of certain types of research, then it is important that the guiding principles not be amended or diluted through notes of clarification but rather it is the behaviour of the research community which needs to change.

2.5 Summary

In compiling this review, I have sought to familiarise readers with the evolving text of the DoH over its nearly half-century of existence. I have raised what I see as

important issues regarding its future but up to now I have avoided one important question. Since time immemorial the medical profession has used codes of ethics to sum up the ethical responsibilities members of the profession take upon themselves in the practice of medicine. Undoubtedly the best known of the ancient codes is the Hippocratic Oath [Leven, 1998]. With respect to ethical codes in medical research the Nuremberg Code and the DoH hold pride of place. The unanswered question is whether the existence of such codes really raises the ethical standards in medical research or whether they are "Only words, words; to be led out to battle against other words" [Lewis, 1956]? The fact that a supposedly rigorous code of medical research ethics existed in Germany from 1931 through to the end of the Second World War [Sass, 1983] raises this question rather starkly and has led Weisstub to caution: "We should not be naïve about the capacity of codes or legislation to bring unanimity and predictability to the subject" [Weisstub, 1998].

Yet there is little doubt that promulgation of the Edinburgh (2000) revision of DoH has sensitised the medical research community to many important issues once again. On the one hand, some may question the value of a document that aspires to such a high ethical standard. On the other hand, it must also be of considerable interest to note the responses of a researcher or an organisation to these aspirations. A very interesting question which deserves much greater consideration is to ask just what is revealed when the response to the text is to seek loopholes and ask, "what can I get

away with?" as opposed to, "How can I seek to achieve these aspirational standards in my research?"

2.6 Personal Perspective

In chapter 6, the detailed results of a series of 57 semi-structured interviews is presented. This focuses on the interpretation of the text of the paragraphs representing the most significant changes made to the DoH in the 5th (Edinburgh, 2000) revision. At the end of each interview, each interviewee was asked to take a moment for personal reflection on how they felt they had come to hold the views that they had expressed since, of course, no-one's views and opinions come "out of nowhere" – my own included.

At this point it is important, therefore, to try to articulate how my own perspectives since all interpretation must come from some perspective – and my interpretation of others' interpretations will be influenced by my own biases. I will attempt to articulate my perspective by considering how I may have responded to the question: "How have you come to hold these views?" – the question that was presented to the interviewees at the end of each interview.

I can recognise two major domains of influences over my own views. The first comes from my training and experience as a medical practitioner. My career spanned both general practice and the specialty of public health medicine before eventually focusing on the latter. The perspective afforded by the former of these two areas of work gave me an acute sense of both the needs of the individual patient

and their families. The second, in particular the science of epidemiology which underpins the science of public health practice, gave me a strong sense of the importance of the evidence-base for health care if we are to maximise benefit and minimise harm both to the individuals who seek medical care and to the communities in which they live. The tension between the need to build this evidence-base through research while at the same time fully taking into account the needs, the rights and the respect due to each individual patient and community is at the heart of my understanding of the debate surrounding medical research ethics. In using the word "tension", I do not imply that I think the individual is necessarily at odds with science and society's efforts to improve the evidence-base. Often the interests of science, the interests of society and the individual's interests pull in the same direction. However, there can be divergence in these and where such divergence exists, the ethical tensions are most acute.

The second major domain of influence comes from my own spiritual/faith pilgrimage and the opportunity I've had to undertake a masters degree in a theological discipline (specifically, New Testament Studies). I therefore approach this study with a perspective that *texts do matter; texts change the world in which we live.* Those familiar with the lead-up to the Iraq War that began in 2003 may recall how much debate centred around the term "material breach" that an earlier United Nations resolution had imposed on Iraq following the 1990 invasion of Kuwait and the "1st Gulf War". The point here is not to debate the rights or wrongs of the actions taken by various nations but to recall this as an example of a text changing the world.

Whether one takes the "cynical" view that once those in power have decided on a course of action, the text is simply used as a justification for that action, or whether one actually believes that a respect for the text influences decision-making doesn't really matter here. Either way, the text has exercised minds and consumed resources – intellectual and financial – as people have sought to wrestle with the possible interpretations of the words.

The Declaration of Helsinki is also a text that I believe, in a similar vein, has "changed the world". Whether or not an individual believes that it actually changes the behaviour of those involved in medical research, the simple fact that it has exercised the minds of those trying to interpret it has, in some way, changed those individuals. As the above chapter, and those to follow will show, a great deal of effort and thought and time on the part of many leaders in the medical world from many nations has gone into the interpretation of the text of the Declaration of Helsinki and the focus of this thesis will be on those interpretation difficulties and challenges.

My perspectives and understanding of the ethical dilemmas involved in building, through research, an evidence-base for providing health care has changed through conducting this study and continues to change. Although I have sought to investigate and analyse the interpretations of others with respect to the text of the DoH, I cannot escape the interpretive frameworks that I bring to such an analysis. My understanding is therefore always an "interpretation of interpretations". In trying to explain, as I have above, my understanding of the main influences on my

interpretive framework I hope thereby to enable those reading this analysis to come to their own conclusions about the interpretive biases that I have, no doubt, brought to this work.

2.7 Epilogue

The material from the above chapter was published in British Journal of Clinical Pharmacology 2004; 57 (6): 695-713 under the title *The Text of the Declaration of Helsinki: Past, Present and Future.* Three appendices were published with this paper and they appear also as appendices in this thesis. They are: Appendix 1 – text of Nuremberg Code (1947); Appendix 2 – text of 1st (Tokyo, 1975 revision) of DoH; Appendix 3 – text of 5th (Edinburgh, 2000 revision) of DoH.

3. WHAT CHANGED FROM THE 4TH (SOMERSET WEST, 1996) TO THE 5TH (EDINBURGH, 2000) REVISIONS?

CHAPTER 3: WHAT CHANGED FROM THE 4TH (SOMERSET WEST, 1996) TO THE 5TH (EDINBURGH, 2000) REVISIONS?

3.1 Introduction

To consider the impact of the 5th revision it is necessary to consider in detail what changes took place between these versions. What follows is a detailed paragraph-by-paragraph analysis of the changes. This has two functions. First, it illustrates why certain changes were emphasised in the previous chapter. Second, it provides the rationale for the choice of paragraphs that were to be the focus in the semi-structured interviews that provide the empirical data, the analysis of which is presented in detail in Chapter 6.

This section seeks to explicate the origins of the current version of the Declaration of Helsinki, i.e. the version that was adopted by the WMA in October, 2000 in Edinburgh, Scotland. When this version is specifically being compared with earlier versions it will be referred to as the "Edinburgh Version." Otherwise, when I refer to the "Declaration of Helsinki", it will mean either the most recent (i.e. Edinburgh) version or the entire process of development of the document from its inception in 1964 to the current version. The focus of this paragraph-by-paragraph review is on what changed from the 4th to the 5th revisions. However, there will be occasional

references to earlier versions as well. Before beginning the analysis by paragraph however, it is important to describe in detail the change to the structure of the DoH.

3.2 Structure of the Declaration of Helsinki

The Edinburgh Amendment has only three section headings compared with the four headings in the previous version. The "Introduction" section remains, although in the Edinburgh Amendment it appears as a series of numbered points rather than the normal prose of earlier versions.

The second section of the Edinburgh Amendment has been re-titled "Basic Principles Applying to All Medical Research." There is no longer a distinction made between "Clinical Research" (i.e. involving patients) and "Non-Clinical" or "Non-therapeutic" research involving healthy volunteers. In earlier versions the logical structure of the document was as follows:

(I) Basic Principles		All Research
(II) Clinical Research	}	- separate entities the
(III) Non-Clinical Biomedical Research	}	sum of which comprises
		"All Research"

The Edinburgh Amendment has sought to ameliorate this situation with the following structure:

Basic Principles Applying to All Research – combining I and II above as well as anything in III which also pertains to I and II

Additional Principles for Medical Research Combined with Medical Care – which contains anything that previously would have been unique to III

3.3 Paragraphs of the Declaration of Helsinki

There are 32 paragraphs in the Edinburgh Revision and what follows is a review of the origin of the content of the most recent review; these origins are based on earlier versions of the Declaration of Helsinki and, in some cases, in the Nuremberg Code. The primary focus is on what has changed from the previous (4^{th}) revision (Somerset West, South Africa) revision of each paragraph. I will refer to this as the 4^{th} revision. However, the earlier versions of the text are also analysed to show how the text has changed over each revision. The text of the paragraph is shown in italics under each heading.

3.3.1 Section A. Introduction (Comprising Paragraphs 1-9)

3.3.1.1 Paragraph 1

"The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data."

This paragraph demonstrates considerable modification from the previous version of the Declaration. The opening sentence about the origin and purpose of the Declaration of Helsinki has been moved to the beginning of the document. Previously it was to be found in the 8th (and final) paragraph of the Introduction to the 4th Amendment. In that version, the case for the need for such a document is built up through the first seven paragraphs. The recognisable origin to Paragraph 1 of the Edinburgh revision is the preamble to previous versions: "the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects". This has now been transferred to the body of the document. The second sentence of Paragraph 1 is entirely new to the Edinburgh revision.

3.3.1.2 Paragraph 2

"It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty".

There are two changes in this Paragraph from the 4th revision:

1. "His or her knowledge" (4th revision) is replaced by "the physician's knowledge."

2. The word "mission" has been replaced with the word "duty".

3.3.1.3 Paragraph 3

"The Declaration of Geneva of the World Medical Association binds the physician with the words, 'The health of my patient will be my first consideration,' and the International Code of Medical Ethics declares that, 'A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient'."

This is unchanged in wording from the 4th revision. It occurs in the 2nd paragraph in the 4th revision. The move to 3rd position in the Edinburgh revision is occasioned by the shift of the material in Paragraph 1.

3.3.1.4 Paragraph 4

"Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects".

The statement has not changed in wording from the 4th amendment to the Edinburgh Amendment. It has moved from 5th paragraph in the "Introduction" to 4th paragraph. This phrase no longer follows the statement regarding "risks and burdens" which now occurs in Paragraph 7 (see below).

3.3.1.5 Paragraph 5

"In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society".

This paragraph occurred in the 4th amendment in the "Basic Principles" section, Paragraph 5b. In addition, "concern for the interests of the subject" now reads "considerations related to the well-being of the human subject" and "must always prevail" (4th revision) now reads "should take precedence".

In addition, the 4th revision, under the (now defunct) section entitled: "Non-therapeutic Biomedical Research Involving Human Subjects (Non-clinical Research)" contained the statement "In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject" (Paragraph III.4).

From a logical perspective, these statements seem to mean the same thing though grammatically they are stated very differently. There is now, in the Edinburgh revision, only one statement to this effect.

3.3.1.6 Paragraph 6

"The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality".

The first sentence of this paragraph is unchanged from the 4th amendment of the Declaration of Helsinki. However, the second sentence is entirely new in the

Edinburgh Amendment and appears to represent a significant change in the expectation to undertake research.

3.3.1.7 Paragraph 7

"In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens".

This sentence is unchanged from the 4th amendment. It occurs at a slightly later point in the Edinburgh Amendment than in the 4th amendment (where it is the 4th sentence). In both versions it follows the same sentence/paragraph.

3.3.1.8 Paragraph 8

"Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care".

This paragraph is entirely new in the Edinburgh Amendment of the Declaration of Helsinki.

3.3.1.9 Paragraph 9

"Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects".

The following statement occurs in the 4th amendment: "It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are

not relieved from criminal, civil and ethical responsibilities under the laws of their own countries." These two sentences are in fact the same in the 2nd (Venice) and 3rd (Hong Kong) amendments. In the original Declaration of Helsinki of 1964 and the 1st amendment (Tokyo) the only difference in wording was the second sentence referred to "Doctors" rather than "Physicians". The Nuremberg Code does not contain any such material. This is a sea-change in terms of how the Declaration of Helsinki views itself and its scope.

3.3.2 Section B: "Basic Principles for All Medical Research" (Comprising Paragraphs 10-27)

The introductory section of the Edinburgh Amendment concludes with Paragraph 9. What follows are the origins of what is now Paragraphs 10-27 of the Edinburgh Revision. As mentioned above, the 5th revision has put an end to what was envisaged in previous versions as the dichotomy between "Clinical" and "Non-clinical" research upon which the structure of the document was based.

3.3.2.1 Paragraph 10

"It is the duty of the physician in medical research to protect the life, health, privacy and dignity of the human subject".

This is a completely new paragraph in the Edinburgh Amendment.

3.3.2.2 Paragraph 11

"Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature,

other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation".

This sentence has been reworked somewhat from the 4th amendment where it occurs as the first statement under the heading of "Basic Principles" and reads: "Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature".

3.3.2.3 Paragraph 12

"Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected".

This sentence was introduced into the Declaration of Helsinki at its 1st revision in 1975. It remained unchanged until the Edinburgh Amendment where the word "appropriate" was substituted for "special". Significant change to the placement of this sentence has occurred. In earlier versions this sentence was in the "Introduction" but now it occurs as the 3rd Paragraph of the "Basic Principles for All Research" section. This seems appropriate as the content seems to state a "basic principle" rather than to make an introductory statement.

3.3.2.4 Paragraph 13

"The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the

right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects".

This is the longest paragraph of the document, perhaps reflecting the importance placed upon the process of ethics committee review of research protocols. It has considerably increased in detail and complexity over its counterpart in the 4th amendment. This is reflected by the word count (115 words vs. 63). Clarity has been improved in presentation. The paragraph now contains 5 succinct sentences whereas in the 4th amendment all 63 words comprised one complex sentence.

The requirement for description of each experimental procedure in a protocol first entered the Declaration at the 1st revision in Tokyo, 1975. Here it comprised one 34-word sentence: "The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance". It remained unchanged in the 2nd (1983) revision. At the 3rd (1989) revision, the requirement that the committee be independent of both investigator *and* sponsor was added as well as the clause relating to conformity with the laws and regulations of the country in which the research is performed. This paragraph was then unchanged in the 4th (1996) revision by which time it read: "The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which

should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed".

Therefore it can be seen that the following elements have been added in the Edinburgh Amendment:

1. The "specially appointed committee" is now known as a "specially appointed ethical review committee";

2. In addition to the provision of "consideration, comment and guidance" this committee should also have power to approve (where appropriate) or (by logical extension) not approve the protocol;

3. The independence of the committee from investigator and sponsor is broadened to include "any undue influence";

4. The committee has the right (interestingly NOT an obligation) to monitor ongoing trials;

5. The investigator is explicitly obliged to provide ongoing monitoring information to the committee and is to report any serious adverse events to the committee;

6. Detailed information must be provided to the committee covering any potential conflicts of interest and details of incentives to subjects must also be disclosed for the committee to review.

3.3.2.5 Paragraph 14

"The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration".

There is a minor change in wording and a significant change in position in this paragraph from the 4th revision to the Edinburgh Amendment. The phrase "should indicate that there is compliance with the principles enunciated in this Declaration" (Edinburgh) replaces "should indicate that the principles enunciated in the present Declaration are complied with". The only nuance of meaning that changes occurs with the omission of the word "present". This seems curious in that there is a loss of emphasis that the Declaration of Helsinki is subject to modification and that it is the current version of the Declaration that the WMA intends to be adhered to.

This paragraph is moved forward significantly in the document. In the 4th revision it occurs as the last statement in the "Basic Principles" section. Given that it refers to a requirement relating to the research protocol, this adds coherence to the document.

3.3.2.6 Paragraph 15

"Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent".

This clause began its existence within the Nuremberg Code (1947) as Paragraph 8: "The experiment should be conducted only by scientifically qualified persons. The

highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment". When adopted into the original Declaration of Helsinki it read "Clinical research should be conducted only by scientifically qualified persons and under the supervision of a qualified medical man". It is unclear why the second sentence was dropped.

In 1975, with a change to non-sexist language and the addition of the second sentence, this clause took the exact wording seen in Paragraph 15 of the Edinburgh Amendment.

3.3.2.7 Paragraph 16

"Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available".

The Nuremberg Code required that "before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation". Communication of these matters implicitly requires the careful considerations which are spelled out in the first sentence of this paragraph.

What now appears as Paragraph 16 began in the original Declaration of Helsinki (1964) in section I (Basic Principles), no. 4: "Every clinical research project should be preceded by careful assessment of inherent risks in comparison to foreseeable benefits to the subject or to others". In the 1st revision (1975) this sentence was changed to "Every *biomedical* research project involving human subjects should be preceded by careful assessment of *predictable* risks in comparison with foreseeable benefits to the subject or to others" [italics added to emphasise the changes]. This was then followed by the sentence: "Concern for the interests of the subject must always prevail over the interest of science and society". This clause was then unchanged in the 2nd, 3rd and 4th revisions of the Declaration. The Edinburgh Amendment saw the second sentence "promoted" to stand alone in Paragraph 5. Additionally there is a change in wording from "biomedical research" (2nd, 3rd, and 4th amendments) to simply "medical research" (Edinburgh Amendment).

3.3.2.8 Paragraph 17

"Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results".

This is a heavily modified version of Paragraph 7 in the "Basic Principles" section of the previous version of the Declaration of Helsinki. That version (1996) read: "Physicians should abstain from engaging in research unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any

investigation if the hazards are found to outweigh the potential benefits". The paragraph is identical in the 1983 and 1989 documents. In the 1975 (1st amendment) the word "physicians" does not occur but rather "doctors should abstain" is the phrase used. No corresponding paragraph appears in the original (1964) Declaration of Helsinki.

3.3.2.9 Paragraph 18

"Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers".

This is a modification of Paragraph 4 in the "Basic Principles" section of the 4th amendment of the Declaration of Helsinki which states: "Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk of the subject". Three points should be noted:

(i) The change in terminology from "biomedical" to "medical" research.

(ii) The change from "disabling" terminology, i.e. "cannot legitimately be carried out" to "enabling" terminology, i.e. "should only be conducted if".

(iii) The addition of the "intensifying" sentence: "This is especially important when the human subjects are healthy volunteers".

3.3.2.10 Paragraph 19

"Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research".

This has been discussed above in chapter 2 and represents one of the more potentially controversial changes in the 5th (Edinburgh, 2000) revision. It represents an entirely new paragraph in the DoH and its evolution through the WMA's processes to its final form in the document is traced in Chapter 4.

3.3.2.11 Paragraph 20

"The subjects must be volunteers and informed participants in the research project"

This sentence is a new addition in the Edinburgh revision although it reflects a "summing up" of many of the other articulated principles relating to consent that have been present in all revisions of the DoH and in the Nuremberg Code.

3.3.2.12 Paragraph 21

"The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject".

This is a modification of Paragraph 6 under "Basic Principles" from the 4th Amendment. Some of the changes involve merely a change in language usage from a singular noun to a plural noun ("the right of the research subject" changes to "the right of research subjects") with the corresponding pronoun change ("his or her" changes to "their"). However the "confidentiality of the patient's information" is a new phrase added to the protections articulated here. It corresponds with the document's explicit inclusion of identifiable medical records into the scope of the

Declaration (Paragraph 1). The clause first appeared in the 1975 version (1st amendment) and was unchanged in 1983 and 1989.

3.3.2.13 Paragraph 22

"In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed."

This is the 2nd longest paragraph in the document and, dealing as it does with the issue of consent, this is perhaps to be expected. It appears in a shorter form as Paragraph 9 under "Basic Principles" in the 4th amendment.

The first sentence is identical in structure to that in the 4th amendment but to the list of items of information provided to potential subjects are added: "sources of funding", "any possible conflicts of interest", and "institutional affiliations of the researcher".

The second sentence has changed from "he or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time". The awkward triple use of the dual pronoun phrase "he or she" has been eliminated in favour of "the subject".

The predicate phrase has also been shortened by a change in the Boolean logic of the sentence. The predicate becomes an "or" clause rather than the more cumbersome "and" with repetition of "and that he or she".

In terms of content, although the intent seems to be the same, the 4th amendment phrasing of "liberty to abstain from participation" changes to "right to abstain". The second part of this sentence changes the wording from "free to withdraw ... consent" to "right ... to withdraw consent". Also of note is the addition of the new phrase "without reprisal" to the sentence in the Edinburgh Amendment.

The final part of the paragraph, dealing with the giving of informed consent and documentation of this is elaborated significantly. The explicit requirement to "[ensure] that the subject has understood the information" is a new addition. Also added is the final sentence which specifies what to do if written consent cannot be obtained.

This paragraph first appeared in its current form in the 1975 version. The only change until the Edinburgh Amendment was replacement of the word "doctor" by "physician" is the sentence about obtaining freely-given consent. The paragraph is a synthesis of several scattered sentences in the 1964 version of the Declaration of Helsinki. In the synthesis several important changes also occurred. For example, the explicit reference to "patient psychology" was dropped (in 1964 the statement "If at

all possible, consistent with patient psychology, the doctor should obtain the patient's freely given consent after the patient has been given a full explanation". However, this sentence occurs in the same paragraph as, and immediately after the sentence referring to the use of "new therapeutic measures" in the 1964 version. This suggests that it was envisaged to apply only to that situation which is now covered in Paragraph 32 of the current version of the Declaration.

The other sentences from the original (1964) Declaration which have been incorporated into this paragraph come from the "non-therapeutic clinical research" section. Various phrases and intentions from Paragraphs 2, 3a, 3b, 3c, 4a, and 4b have been re-worded to compile this paragraph in the 1975 and subsequent versions.

3.3.2.14 Paragraph 23

"When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship".

This paragraph is largely unchanged from Paragraph 10 of the Basic Principles section of the 4th amendment. There is the pronoun change from "his or her" to "the physician" characteristic of the Edinburgh Amendment seen in the first sentence. In the second sentence the adjective "well-informed" is added before "physician". The final change to the wording of this paragraph has been to drop the adjective

"official" from "official relationship" at the end of the paragraph. The paragraph first appeared in 1975 and was unchanged in the 1983, 1989 and 1996 amendments with the exception of the "doctor" / "physician" change with the 1983 amendment.

3.3.2.15 Paragraph 24

"For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons".

This paragraph originates from what was Paragraph 11 under "Basic Principles" in the 4th revision. Because of the complexities of the change, Paragraph 11 of the 4th revision is also reproduced here:

"11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian". (Declaration of Helsinki, 4th (1996) revision)

The first sentence of this paragraph from the 4th revision is present in identical wording in the 1st, 2nd, and 3rd revisions. However, it changed considerably in the 1st (1975) revision from the original wording:

"If at all possible, consistent with patient psychology, the doctor should obtain the patient's freely given consent after the patient has been given a full explanation. In case of legal incapacity consent should also be procured from the legal guardian; in

case of physical incapacity the permission of the legal guardian replaces that of the patient". (DoH, original (1964))

This itself represents a considerable modification from the text of the Nuremberg Code pertaining to consent. Nuremberg thus closed the door for medical research on anyone other than those able to give informed consent and spells out the definition of what such consent is. From the original version of the DoH do we see the occurrence of clauses re-opening that door.

It should also be noted that the final sentence of Paragraph 24 of the Edinburgh revision is entirely new. Changes to the 2nd sentence of the previous (4th) revision of the DoH are discussed under "Paragraph 25".

3.3.2.16 Paragraph 25

When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

This has changed in the following ways from the previous version of the DoH:

(1) The sentence now pertains to all who are legally incompetent, whereas previously it referred only to minors.

(2) The word "assent" has replaced "a consent" (1st occurrence of "assent").

(3) The phrase "about participation in research" has been added.

(4) The words "that assent" have replaced "that minor's consent".

(5) "Legally authorised representative" has replaced "minor's legal guardian".

For completeness a minor change to note is that the 3rd (1989) revision saw a very slight change in wording: "consent" was changed to "a consent".

3.3.2.17 Paragraph 26

Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

This paragraph is entirely new in the Edinburgh revision and continues the complex articulation in the DoH of issues of consent. Although changes are important they do not appear to have given rise to particular controversy although the way the DoH articulates the whole issue of consent for research could make for a lengthy study itself – though beyond the scope of this particular work. Note that the first sentence restates what is asserted in the final sentence of Paragraph 24 but with the syntax reversed from "should not be done, unless" to "should be done only if".

3.3.2.18 Paragraph 27

Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in

accordance with the principles laid down in this Declaration should not be accepted for publication.

There is no mention of the issue of publication of results until the 1st (1975) revision, where Paragraph 8 under "Basic Principles" states:

In publication of the results of his or her research, the doctor is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
Declaration of Helsinki, 1st (Tokyo, 1975) revision

The word "doctor" was changed to "physician" in accordance with this change occurring throughout the 2nd (Venice, 1983) revision. No changes to the text or its position in the Declaration were made in the 3rd or 4th revisions. Thus we can see that the text changed considerably with the Edinburgh revision. The 1st sentence is entirely new. In the 2nd sentence, the phrase "In publication of the results of his or her research" has been pared down with the removal of the grammatically unnecessary "his or her". The 3rd sentence is also completely new to the Edinburgh revision. This addition parallels the similar addition of an explicit requirement to declare potentially competing interest to the ethical review committee (Paragraph 13) and during the informed consent process (Paragraph 22). For the purposes of comparison, Table 4 below shows what is stipulated in the new requirements for disclosure in each of these three situations.

Table 3.1: Comparison of requirements of disclosure of competing interests in various paragraphs of the DoH:

Paragraph 13 (stipulated disclosures to the ethical review committee)	Paragraph 22 (list of stipulated disclosures during informed consent process)	Paragraph 27 (stipulated disclosures on submission for publication of results)
Information regarding: 1. Design and performance of each experimental protocol 2. Funding 3. Sponsors 4. Institutional affiliations 5. Other potential conflicts of interest 6. Incentives for subjects.	Information regarding: 1. Aims 2. Methods 3. Sources of funding 4. Any potential conflict of interest 5. Institutional affiliations 6. Anticipated benefits 7. Potential risks 8. Discomfort entailed	Information regarding: 1. Sources of funding 2. Institutional affiliations 3. Any possible conflicts of interest

3.3.3 Section C: Additional Principles for Medical Research Combined with Medical Care (Comprising Paragraphs 28-32 and Notes of Clarification)

3.3.3.1 Paragraph 28

The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

The content of this paragraph was present in the original (1964) Declaration of Helsinki. Interestingly it represents quite a change in emphasis from the Nuremberg Code. Nuremberg, in its preamble and in Paragraph 2 speaks of research being justified by its potential "for the good of society". No distinction is made in Nuremberg between research conducted on patients where there is a combination of

research activity and treatment activity. Thus there really is no Nuremberg parallel or origin to this paragraph.

In the 1964 Declaration of Helsinki, this paragraph appears as the 2nd (i.e., final) paragraph under the heading "Clinical Research Combined with Professional Care" and reads: *"The doctor can combine clinical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that the clinical research is justified by its therapeutic value for the patient".*

Changes with each revision involved are listed as follows:

1st (Tokyo) 1975: *clinical research* changes to *medical research* but the term "clinical research" remains incorporated in the heading in this section by being included in parentheses at the end, i.e., "Medical Research Combined with Professional Care (Clinical Research). Also changed is the phrase at the end of this paragraph, which became "*clinical research is justified by its potential diagnostic or therapeutic value for the patient".* Additionally the paragraph becomes Paragraph 6 of this section with the addition of much new material in the 1975 revision;

2nd (Venice) 1983: the phrase "*clinical research*" in the paragraph changes back to *medical research*. Additionally the word *physician* replaces the word *doctor* throughout the 1983 revision.

3rd (Hong Kong) 1989: no change

4th (Somerset West) 1996: no change.

This left the 4th revision statement as:

II.6. *The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.*

Thus we can see the following changes with the 5th (Edinburgh, 2000) revision:

1. The word "*can*" becomes "*may*";

2. "*professional care*" becomes "*medical care*";

3. The phrase "*the objective being the acquisition of new medical knowledge*" is dropped completely;

4. The second occurrence of "*medical research*" changes to read simply "*research*";

5. The justification phrase changes from "*potential diagnostic or therapeutic value*" to "*potential prophylactic, diagnostic or therapeutic value*".

6. The phrase at end "*for the patient*" is dropped so this sentence now finishes with the statement above.

7. The 2nd sentence, "*When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects*", is entirely new in the 5th (Edinburgh, 2000) revision.

3.3.3.2 Paragraph 29

The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

This work has already shown, in Chapter 2, and will continue to show as the work unfolds that Paragraph 29 is one of the most controversial of all of the content of the Declaration of Helsinki. Yet its content is by no means radically new in the 5th (Edinburgh, 2000) revision.

The first appearance of any of the wording that gave rise to the current Paragraph 29 appears as Paragraph II.2 in the 1st (Tokyo, 1975) revision: *The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.* Immediately following this in the 1st (Tokyo, 1975), but in a separate paragraph, was the first mention of a control group: "*In any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method*".

These two paragraphs were unchanged until the 4th (Somerset West) 1996 revision. It is in 1996 that the explicit mention of placebo first occurs with the addition of a 2nd sentence to Paragraph II.3: "*This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists*".

Therefore the changes taking place in the 5th (Edinburgh, 2000) revision are as follows:

1. It is now "*the benefits, risks, burdens and effectiveness of a new method*" that should be considered, replacing the old phrase "*The potential benefits, hazards and discomfort of a new method*", i.e., the word *effectiveness* is added and the word *potential* dropped.

2. The indicative pronoun "*against those of*" (referring to the antecedent *benefits, risks, burdens and effectiveness*) replaces the phrase "*the advantages of*" in reference to what is being suggested as the control arm of the study.

3. In line with the rest of the 5th (Edinburgh, 2000) revision, the word *prophylactic* is added before the words *diagnostic* and *therapeutic* in the phrase referring to existing methods.

4. The phrase "*In any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method*" is dropped from this paragraph and recurs in a modified form in Paragraph 30 (see below).

5. In the final sentence of Paragraph 29 the phase "*inert placebo*" is changed to "*placebo, or no treatment*" and the word *prophylactic* is added before *diagnostic* and *therapeutic* as above.

The Note of Clarification to Paragraph 29 will be considered after consideration of all paragraphs of the actual body of the text of the Declaration of Helsinki.

3.3.3.3 Paragraph 30

At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

As we saw under the discussion of Paragraph 29, there is mention of assurance of access to the best proven diagnostic and therapeutic methods in earlier versions of the DoH, dating back to the 1st (Tokyo, 1975) revision. Changes with the 5th (Edinburgh, 2000) revision are listed below:

1. Earlier versions make no mention of the timing of this and the reference to "at the conclusion of the study" is entirely new in the 5th (Edinburgh, 2000) revision;

2. Earlier versions simply said "every patient" where the current revision elaborates this to "every patient entered into the study";

3. The 5th (Edinburgh, 2000) revision states that such patients "should be assured of access" whereas previous versions simply stated "should be assured of";

4. As has occurred at several points in the 5th (Edinburgh, 2000) revision, "best proven diagnostic and therapeutic method" has been elaborated to "best proven prophylactic, diagnostic and therapeutic methods".

5. Finally, but importantly, this reference to access to the best methods has been separated from the text of Paragraph 29.

It will be seen throughout this work that Paragraph 30, along with Paragraph 29, are the most extensively discussed and debated paragraphs of the 5th (Edinburgh, 2000) revision and gave rise to an entirely new genre of text within the DoH – the *Note of Clarification*.

3.3.3.4 Paragraph 31

The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

The first sentence of this paragraph is entirely new in the 5th (Edinburgh, 2000) revision. The 2nd sentence was originally added in the 1st (Tokyo, 1975) revision but the reference was to the *doctor-patient relationship*. The word *doctor* was changed to *physician* throughout the DoH with the 2nd (Venice, 1983) revision and the order of the words was reversed to read *patient-physician relationship*. This sentence is unchanged since 1983.

3.3.3.5 Paragraph 32

In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

This is the final formal *paragraph* of the 5th (Edinburgh, 2000) revision. The origins of this paragraph can be traced to the original (1964) DoH where it occurs as the first

sentence of the section referring to the combination of research with professional care. That version read: "In the treatment of the sick person the doctor must be free to use a new therapeutic measure if in his judgment it offers hope of saving life, re-establishing health, or alleviating suffering". Interestingly, this particular paragraph (II.1) of the original (1964) DoH also contained the sentence relating to informed consent for research, i.e., "If at all possible, consistent with patient psychology, the doctor should obtain the patient's freely given consent after the patient has been given a full explanation. In case of legal incapacity consent should also be procured from the legal guardian; in case of physical incapacity the permission of the legal guardian replaces that of the patient". In subsequent versions of the DoH, this clause relating to consent has been dispersed into other paragraphs relating specifically to consent and how it has been modified is discussed above in relation to the specific paragraphs concerned.

In the 1st (Tokyo, 1975) revision (as well as moving the consent clause elsewhere), the term "new therapeutic measure" was elaborated to "new diagnostic and therapeutic measure" and "his" was changed to "his or her" in line with removal of other male-gender-specific clauses wherever the document refers to physicians. The 2nd (Venice, 1983) revision saw only the change of "doctor" to "physician" in line with the rest of the document and the paragraph remained unchanged through the 3rd (Hong Kong, 1989) and 4th (Somerset West, 1996) revisions.

Thus we can see that the changes with the 5th (Edinburgh, 2000) revisions are as follows:

1. "Treatment of the sick person" is changed to "treatment of a patient";

2. "Diagnostic and therapeutic methods" have been changed to "prophylactic, diagnostic and therapeutic methods";

3. The clause "where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective" has been introduced as justification for the freedom of the physician to resort to untested methods;

4. Reference to consent has been re-introduced to this paragraph with the addition of another qualifying clause prior to the statement of the physician's freedom to use untested methods with the addition of the phrase, "with informed consent from the patient";

5. The phrase "his or her judgment" has been changed to "the physician's judgment";

6. The remaining 3 sentences of this considerably lengthened paragraph are new to the 5th (Edinburgh, 2000) revision of the DoH.

3.3.3.6 Notes of Clarification

Both notes of clarification represent entirely new additions to the most recent version of the Declaration of Helsinki. These two notes do not only represent the addition of entirely new sentences to the Declaration. They additionally represent the addition of an entirely new *sub-genre* of text..

In a break with the nomenclature used on the WMA website, the Notes of Clarification are referred to as part of the 5th (Edinburgh, 2000) revision as they are addenda to this version of the Declaration which is otherwise unrevised. The first Note of Clarification to Paragraph 29 was added in 2002 and the Note of Clarification to Paragraph 30 was added in 2004. For the sake of presenting in this section the complete text with which this entire dissertation is concerned the two Notes of Clarification are presented below. No further analysis is presented in this section, analysing as it does the origins of the text, because both Notes are entirely new to this version of the DoH.

3.3.3.6.1 Note of Clarification to Paragraph 29

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:
- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.
All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

3.3.3.6.2 Note of Clarification to Paragraph 30

The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

This is included at this point merely for completion of the entire 5th (Edinburgh, 2000) revision of the DoH as its addition to the text post-dated all of the data collection for the semi-structured interviews, the results of which are described in chapter 6. This is the text, as a whole, therefore, that was considered in the 6th revision.

3.4 Summary

One of the main reasons for a detailed consideration of the text was to detect those changes that should be the subject of the qualitative semi-structured interviews, the results of which are described in Chapter 6. It has already been seen that Paragraphs 19, 29 and 30 would need to be included.

Detailed consideration of the above and consultation led to the conclusion that, in addition to Paragraphs 19, 29 and 30, already seen in the literature survey in chapter 1 (above) as the most controversial paragraphs, that the most significant additional features of the 5th Revision of the DoH were as follows:

> Paragraph 1: Addition of identifiable tissue and human material to the document's scope;

Paragraph 6: A vastly enhanced statement of the responsibility to undertake research;

Paragraph 9: A complete overhaul of how the DoH views its own authority;

Paragraph 27: The statement of the requirement to publish negative as well as positive results as a clear-cut ethical requirement.

In addition, the change to the logical structure of the document and elimination of the section on "Non-therapeutic research" seemed also to be of great importance. Thus these became the focus of the semi-structured interviews, the methodology and results of which are discussed in Chapter 6.

4. BEHIND THE SCENES IN THE REVISION PROCESS: WHAT LESSONS CAN BE LEARNED?

CHAPTER 4: BEHIND THE SCENES IN THE REVISION PROCESS: WHAT LESSONS CAN BE LEARNED?

4.1 Prologue

This chapter seeks to explain the workings of the WMA in drafting, adopting and revising codes of ethics with specific reference to the revisions that led to Paragraphs 19, 29 and 30 of the 5th (Edinburgh, 2000) revision of the Declaration of Helsinki. This chapter begins with a review of the history of the text.

4.2 Introduction

In this chapter I seek to summarise how the text of the Declaration of Helsinki (DoH) came into its current form. I will briefly describe the changes with the first four revisions from the original 1964 version and then consider in more detail the discussions leading up to the 5th and current revision of the Declaration of Helsinki. This revision has given rise to considerable controversy and I will focus on what are the three most controversial paragraphs (Paragraphs 19, 29 and 30) in the current version. I make use of archival material made available by the World Medical Association (WMA) to trace in detail how these particular paragraphs evolved. By undertaking this analysis, I have the twofold aim of exploring in further detail the

apparent ethical intentions behind these paragraphs and to consider what lessons this process may provide when the DoH, at some point in the future, is further revised.

4.3 The Evolution of Previous Versions of the Declaration of Helsinki

In September 1964, the WMA officially published in its quarterly journal, the World Medical Journal, the text of the original DoH [WMA, 1964]. Sev Fluss has undertaken a detailed comparison of the DoH with the Nuremberg Code of 1947 and notes the extensive influence of Nuremberg on the DoH. In a detailed analysis, Herranz identifies within the Nuremberg Code's ten paragraphs, twelve statements that serve as markers to determine whether a particular medical experiment conformed to appropriate ethical standards. He noted that ten of these twelve markers from Nuremberg are retained in the DoH [Fluss, 1999]. The original DoH, at just over 700 words in length, was a very brief document when compared with future (and the current) revision(s).

A detailed analysis of how the text of the DoH changed with each of the revisions is presented above in Chapter 2 (see 2.2 Declaration of Helsinki: Past). To recap, there was a major revision in 1975. In fact, in percentage terms, the 1975 revision represented a greater change to the text than did the 2000 revision. The revisions of 1983, 1989 and 1996 represented represented relatively minor changes to the text.

4.4 The Fifth Revision of the Declaration of Helsinki: Edinburgh, 2000

The process for the fifth revision of the Declaration of Helsinki lasted from September 1997 to October 2000. It began with a submission by the American Medical Association (AMA) to the WMA Council and finally ended with the near unanimous adoption of the revised form of the Declaration of Helsinki at the WMA Assembly in Edinburgh, Scotland in October 2000. The process essentially went through three major phases, the first two of which proved largely to be "false starts". It was decided in 1998 not to proceed with the version proposed by the AMA but rather to convene a Working Group, chaired by Robert Levine of Yale University to consider the proposed revision of the DoH. Once again, in 1999, the WMA decided against accepting the revision proposed and assembled a new working group in April 1999. This group comprised Nancy Dickey of the United States, Kati Myllymäki of Finland, and Judith Kazimirski of Canada [Williams, 2004].

These three became colloquially known as the "three wise women" and it was their committee's deliberations that eventually provided the basis for the 2000 revision of the DoH. This Working Group reported to the Medical Ethics Committee of the WMA Council. The central focus of the analysis in the remainder of this chapter will be to consider the evolution of the text of what eventually became the three controversial paragraphs (Paragraphs 19, 29 and 30) as the Working Group deliberated, reported to the Medical Ethics Committee (MEC), and received

modifications based on the outcome of MEC and WMA Council meetings. To understand more fully the process, it is necessary to describe in further detail the operating procedures of the WMA and it is to this description that I now turn.

4.4.1 An Aside: World Medical Association Procedures for Drafting and Adopting Ethical Declarations

The process by which the WMA adopts Declarations has been described by Lurie and Greco as "quasi-democratic" [Lurie & Greco, 2005]. This is in contrast to a fully democratic, "one person-one vote" procedure. In this section, I aim to describe more fully the WMA's "quasi-democratic" process. It is through this process that the text of the Declaration of Helsinki passed to take on its current form. To understand the process requires some understanding of the structure of the WMA.

To finally become a Declaration of the World Medical Association, a Declaration must be approved at the WMA's annual assembly. Annual assemblies are usually held in October of each year. The delegates to the annual assemblies are representatives of the constituent National Medical Associations (NMAs) that form the membership of the WMA.

Within the WMA there are six WMA regions: Africa, Asia, Europe, Latin America, North America and the Pacific. It is intended that the venue for the annual assembly rotate through the six regions although for a variety of reasons, a strict order of

rotations is not always followed. (For example, in 2001, the events of September 11 and the subsequent disruption to travel necessitated the cancellation of the planned annual assembly in New Delhi though the WMA Council did manage to meet at WMA Headquarters in Ferney-Voltaire, France.)

As mentioned above, regular members of the WMA are not individuals but the NMAs of the various member countries. It is possible for individual physicians to join the WMA as associate members. The associate members meet just prior to the Assembly and at this meeting they elect two representatives to the General Assembly. These representatives have the right to speak but not to vote.

A current list of the *national* medical association members (NMAs) is available on the WMA's website [WMA, *Members List*, 2011]. The "quasi-democratic" voting process [Greco & Lurie, 2005] means voting strength is weighted according to the "declared" number of members that each national medical association has. An individual national medical association can "declare" any number of members up to its actual number of members. The reason why an NMA would choose to declare fewer than its actual number of members is that the dues paid for WMA membership are linked to the number of declared members. Such an arrangement permits countries whose NMA has a relatively large membership (because of the large population of the country even taking into consideration the higher population:doctor ratio often observed in resource poor countries) but has limited financial resources to

"declare" fewer members. This allows some NMAs to participate in the WMA that would otherwise be unable to do so.

Individual NMAs must weigh the advantage of lower membership dues against the advantage of declaring the full number of members and receiving its full voting strength (and perhaps a place on the WMA Council – see below).

4.4.1.1 WMA Council

The WMA Council meets three times a year: usually in May at a venue near the WMA headquarters and in September or October, immediately prior to and immediately after the Annual Assembly. Although individual NMA members could, in theory, table a motion or resolution on the floor of the Assembly, the chances are very small that it would be accepted if it had not already been discussed and endorsed at a Council meeting (and the Committee stages – see below). Council meetings are both more frequent and longer, allowing much more scope for detailed debate than at the Annual Assembly.

Each of the six WMA regions must always have at least one representative from at least one of the six NMA regions. These regional representatives are elected for a period of two years at a time. Additionally, any NMA with 50,000 or more "declared" members (see above) is also entitled to a seat on the Council. Therefore,

the Council tends to have more representation from countries with relatively large populations, whose NMAs are financially relatively well off.

4.4.1.2 The Medical Ethics Committee

There are three standing committees of the WMA: the Finance and Planning Committee, the Socio-medical Affairs Committee, and the Medical Ethics Committee. Membership of these three standing committees is drawn from the membership of the Council. Each of the three committees meets during Council sessions. With respect to the text of its Declarations, it is the job of the latter two committees to undertake the detailed "word-smithing" required and to bring to the full Council the recommended text of Declarations pertaining to socio-medical issues, or to medical ethics issues respectively. Where the Council cannot agree on the wording of a document, it will usually refer the document back to the relevant committee. In cases where there are deep divisions over the wording of a Declaration, or where a very important Declaration is put forward for major revision, an ad hoc Working Group may be formed that will draw up the text of a document for discussion, first at the Standing Committee stage and, subsequently at the Council stage. Such Working Groups will always canvass individual NMAs for their opinions. In some cases, including the revision of the Declaration of Helsinki, and the note of clarification to Paragraph 30, the WMA will canvass opinion more

broadly and invite comment from a wide range of experts whose interests impinge upon or are impinged upon by the text of the Declaration.

4.4.1.3 Voting Procedures

In both Council meetings and in the Standing Committees, each NMA member has one vote and a simple majority is required for resolutions to be passed. This situation changes completely at the Annual Assembly. Prior to the Assembly there is always a "credentialling" meeting. At this meeting, those NMAs who have paid the appropriate dues for the number of "declared" members are allocated their number of votes. Every NMA has at least one vote. For those with more than 10,000 "declared" members, an additional vote is allocated for each 10,000 "declared" members. Thus, for example, an NMA with 50,000 declared members would have six votes (assuming they had paid the appropriate membership dues by the time of the Assembly).

For resolutions at Assembly that do not relate to medical ethics a simple majority of these allocated votes suffices for the resolution to pass. A resolution to adopt or amend any of the WMA's ethics documents requires 75% or more of these votes.

To be revised in October 2000 the Declaration of Helsinki had to pass through all of the procedures described above. Voting at Council is done by a show of hands. At

the Assembly it is done by a show of cards, each one printed with the number corresponding to that delegation's voting strength. The particular voting decisions of NMAs are not officially recorded by the WMA. All we can be certain of is that the text of any revision of the Declaration of Helsinki received at least 75% voting support although the decision to adopt the text of the Declaration has been described as "near unanimous" [Williams, 2004].

4.4.2 The Evolution of the "Controversial" Paragraphs

Most of the contention that arose out of the fifth (Edinburgh, 2000) revision surrounded three paragraphs – Paragraphs 19, 29 and 30 [Williams, 2004]. That Paragraphs 29 and 30 raised a storm of controversy is evidenced by the WMA's unprecedented step of issuing notes of clarification to these paragraphs. Paragraph 19 was considered for a note of clarification but the final decision was that such a step was unnecessary. The final versions of these three paragraphs are as follows:

> Paragraph 19: Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
>
> Paragraph 29: The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

> Paragraph 30: At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

It is our aim at this point to consider, based on the material that was available in the WMA archives, how these three paragraphs evolved through the process of drafting the text. This analysis is based on unpublished documents made available to me by the WMA. The WMA kindly allowed me free search of their archives. However, because of limited space, limited staff numbers and a recent relocation of the headquarters, the archives were not systematically filed. Some relevant documents appear to be no longer extant – at least in the WMA archives.

The series of documents available that tracked the evolution of the text are all entitled "Proposed Revision of the Declaration of Helsinki" and are serially numbered as follows: 17.C/WW1/2000, 17.C/WW2/2000, 17.C/WW3/2000, 17.C/WW4/2000 and 17.C/WW5/2000. From the minutes of the WMA General Assembly in Edinburgh, 2000 it became apparent that the version presented to the Assembly was 17.C/WW8/2000. This was unchanged in the Assembly so the text of 'WW8' corresponds to the actual text of the fifth revision of the Declaration of Helsinki. Documents 17.C/WW6/2000 and 17.C/WW7/2000 are not extant in the WMA archives and the possible reason for this is discussed below. Although the deliberations of the Working Group began in 1999, documentation of these deliberations is unavailable. I begin therefore with the text of the proposed revision

(17.C/WW1/2000) that was presented by the Working group to the Medical Ethics Committee at the WMA Council meeting in May 2000.

4.4.2.1 May 2000 – 17.C/WW1/2000

The status of the three paragraphs was as follows:

Paragraph 19: This paragraph was not yet in the proposed text.

Paragraph 29: "24. In any medical study, every patient – including those of a control group, if any – should be assured of proven diagnostic and therapeutic methods. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.
23. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods".

This document had what eventually became Paragraph 29 numbered as Paragraphs 24 and 23. The order of occurrence of what were previously Paragraphs II.2 and II.3 in the 1996 version has been reversed (and this accounts for the numbering 24. and 23. in this document). With respect to the wording, what is labelled here as Paragraph 24 is very similar to the 1996 version that reads: "In any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists". The wording of what is labelled here as Paragraph 23 is unchanged.

Comment: The only proposed change therefore at this stage was to require assurance of "proven … methods" rather than the "best proven" method.

Paragraph 30: This paragraph was not yet in the proposed text.

This document was considered by the Medical Ethics Committee and changes were made. The next version (17.C/WW2/2000) was presented by the MEC to the WMA Council. This Council meeting was held shortly after the MEC during the series of meetings on 4-5 May 2000.

4.4.2.2 May 2000 - 17.C/WW2/2000

The text as proposed by the MEC to WMA Council was as follows:

Paragraph 19: "Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research".

Comment: What eventually became Paragraph 19 is now included in the proposed text. The documentation indicates that the text initially proposed by the MEC was "Medical research is only appropriate…" and the word appropriate was changed to "justified" during the MEC meeting.

In this document this paragraph is numbered Paragraph 24a. Apparently it had originally been included as a preamble to the statement about placebo controls. It

was subsequently separated from this statement and moved forward in the DoH to be in the section entitled "Basic Principles (for All Medical Research)".

Paragraph 29: "24b. In any medical study, every patient – including those of a control group, if any – should be assured of proven effective prophylactic, diagnostic, and therapeutic methods.
24c. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists
23. The potential benefits, risks and discomfort of a new method should be weighed against the advantages of the best current prophylactic, diagnostic and therapeutic methods".

Comment: It can be seen that what entered these deliberations as Paragraph 24 has emerged in three pieces, i.e., 24a, 24b and 24c. Paragraph 24a, as mentioned, was moved to a place earlier in the proposed text. 24b and 24c are still consecutive. The only change to the wording of 24b or 24c is the addition of the two words "effective prophylactic". The previous version therefore required assurance of "proven diagnostic and therapeutic methods". It was now proposed to require assurance of "proven effective prophylactic, diagnostic and therapeutic methods".

In what is labelled here as Paragraph 23, the word "hazards" has now been changed to "risks" and the word "prophylactic" added so that the phraseology matches that of Paragraph 24b.

Paragraph 30: This paragraph was not yet proposed in the text.

The above changes were then deliberated by the WMA Council and the ensuing text (17.C/WW3/2000) was approved for distribution by the Council to the various NMAs.

4.4.2.3 May-October 2000: 17.C/WW3/2000

Some minor changes were made to other portions of the proposed text but no changes were made to any of the texts described above under 17.C/WW2/2000. Thus with respect to what eventually became Paragraphs 19, 29 and 30: there is no difference between WW2 and WW3 in the series of documents under consideration. It was the text of 17.C/WW3/2000 that was then released to the various NMAs and further comment invited. The Working Group along with the then Secretary-General of the WMA, Delon Human, then met in August 2000 to consider the proposed revision in the light of these further comments. They presented the updated proposed text (17.C/WW4/2000) based on these deliberations and this text was to be considered by the MEC in early October prior to the pre-Assembly Council meetings.

4.4.2.4 October, 2000: 17.C/WW4/2000

Paragraph 19: "24a. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research. The protocol presented to the review committee

must include a realistic plan to deliver those treatments identified through such research to the populations from which the subjects have been drawn".

Comment: This proposed paragraph now contains a newly drafted second sentence.

Paragraph 29: "24b. In medical research, every patient – including those of a control group, if any – should be assured of the best proven prophylactic, diagnostic and therapeutic methods. This does not exclude the use of inert placebo in studies where no proven prophylactic, diagnostic or therapeutic method exists.
23. The potential benefits, risks and discomfort of a new method should be weighed against those of the best current prophylactic, diagnostic and therapeutic methods".

Comment: What were previously Paragraphs 24b. and 24c. have now been combined into one Paragraph 24b. The word "effective" has been replaced by "the best" so that patients are now to be assured of "the best proven prophylactic, diagnostic and therapeutic methods". This in fact restores the wording (with the exception of the addition of "prophylactic") of the adjectival portion of the sentence to what it was in the 1996 version of the DoH.

In Paragraph 23 the indicative pronoun "those" has replaced "the advantages". "Those" makes reference to "benefits, risks and discomfort". Interestingly, the logic of the previous form of the sentence would have required that the "potential benefits, risks and discomfort" of a new method were weighed only against "the advantages" of the existing method. This potential inconsistency had been present in the DoH since 1975.

Paragraph 30: There remains no mention of the issue that would eventually appear as Paragraph 30 in the revised Declaration of Helsinki. We can see that it did not emerge completely *de novo* but rather appears to be a re-interpretation of the implications of the former 24b., i.e., "In medical research, every patient – including those of a control group, if any – should be assured of the best proven prophylactic, diagnostic and therapeutic methods". This is the version that was considered by the Medical Ethics Committee (MEC) in its deliberations just prior to the General Assembly in Edinburgh in October 2000.

4.4.2.5 October 2000: 17.C/WW5/2000

As mentioned above there is no trace of documents 17.C/WW6/2000, 17.C/WW7/2000 and 17.C/WW8/2000 in the WMA archives. However, as the minutes of the Assembly indicate 17.C/WW8/2000 was the version adopted by the WMA Council and recommended to the WMA General Assembly. Since no changes were made at the Assembly, it can be concluded that WW8 was identical to the adopted text of the revised Declaration of Helsinki.

The MEC met for long hours in the days leading up to the General Assembly in an attempt to finalise the wording of the revision of the Declaration of Helsinki. Working documents were created very quickly at various points in the deliberations and changes were ongoing. The following indicates the status of the text of the three

paragraphs under consideration according to the working document 17.C/WW5/2000.

Paragraph 19: "24a. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research".

Comment: The proposed second sentence requiring a "realistic plan to deliver" treatments identified as beneficial to the population has been removed. This sentence has now reverted to exactly the same wording as proposed by the MEC to the Council in May (see WW2 above). This is also the exact wording of what became Paragraph 19 in the revised DoH. Therefore we can conclude that even if the non-extant WW6 and WW7 contained any differences, they were restored to this text by WW8.

Paragraph 29: "23. The potential benefits, risks and discomfort of a new method should be weighed against those of the best current prophylactic, diagnostic and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists".

Comment: This paragraph has been extensively restructured from the previous version. The entire sentence relating to "assurance of access" has been removed (and the issue of assurance of access now appears in what was to become Paragraph 30 – see below). The sentence beginning "The potential benefits…" is unchanged from its earlier version but it has now been placed before the sentence beginning "This does not exclude…".

Paragraph 30: "24b. At the conclusion of the study, every patient in the study should be assured of access to the best proven prophylactic, diagnostic or therapeutic methods identified by the study".

Comment: This is the first appearance, at this late stage, of what became the controversial Paragraph 30. It was initially a re-wording of the sentence formerly seen as Paragraph 24b (see above).

4.4.2.6 October 2000 – the Fifth Revision of the Declaration of Helsinki, Edinburgh, 2000.

Paragraph 19: Apart from the re-numbering of the paragraph from its interim number 24a to its final position at 19 – a task that could only be finalised when the wording of the Declaration was finalised – there was no change to this paragraph.

Paragraph 29: "The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists".

Comment: Between the working document 17.C/WW5/2000 and the final version of the revised Declaration of Helsinki the phrase "the potential benefits, risks and discomfort should be weighed against..." was changed to "The benefits, risks, burdens and effectiveness of a new method should be tested against...". This represents 3 changes: (i) the word "potential" is removed; (ii) the more metaphorical verb "weighed" (medical research does not usually involved actually determining the weight of the new treatment under investigation) is changed to the more literal

"tested"; (iii) the word "effectiveness" has been added to the list of attributes of the new method that need to be tested against the existing method.

Paragraph 30: "At the conclusion of the study, every patient in the study should be assured of access to the best proven prophylactic, diagnostic or therapeutic methods identified by the study".

Comment: Apart from finalising the paragraph number (see comment above), no changes were made from 17.C/WW5/2000.

4.5 Lessons from the Fifth Revision of the Declaration of Helsinki

I have now traced in detail the evolution of the text of the three controversial paragraphs of the Declaration of Helsinki. It is time to reflect on some of the lessons that can be learned from this analysis.

1. How important is the original intent of the authors of the Declaration of Helsinki? I have already observed the structure of the WMA. It is the largest global grouping of doctors. The efforts of the WMA represent a much sought after international consensus as to what is and what is not ethically acceptable in the conduct of medical research. As such, ethical proclamations by this organisation must be taken seriously. Through this analysis, we can take steps to get closer to understanding the intent of the authors of this Declaration.

2. It must be remembered, however, that once the deliberations of the WMA become fixed in the text of the Declaration of Helsinki that the text can take on a proverbial "life of its own". Although the WMA have been very open and generous in allowing access to their meetings and archives, for the most part those who will read, interpret and apply the Declaration of Helsinki will not be party to these deliberations. Therefore, it is also important that the text can stand alone and be interpreted by its readers in such a way that there is an understanding of what the ethical guidelines established by the Declaration of Helsinki mean in actual research practice. The notion of whether the meaning of a text lies in its author's intent, in its reader's interpretation or, indeed, somewhere else, remains a complex and vexed philosophical problem. It is reasonable to assert that, despite this, it is certainly disingenuous to deliberately misinterpret the author's intent. For example, an overly literal interpretation of Paragraph 19, requiring a reasonable likelihood of benefit to populations from which research subjects are drawn, could lead to the conclusion that research on populations of "healthy volunteers" was ruled out. It seems, however, that the explicit mention of research in "healthy volunteers" (Paragraphs 16 and 18) and "those who will not directly benefit" (Paragraph 8) would mean that such an interpretation represents a decontextualisation and misinterpretation of the intent of the paragraph.

3. There are hazards involved in drafting a document "by committee". The sudden appearance of Paragraph 30 seemed to have taken the medical research community

by surprise. The great difficulty involved in developing a Note of Clarification (the process took 4 years compared with 1 year for Paragraph 29) may be a reflection of the fact that the implications of this paragraph were not subject to the same process of consultation with NMAs and others that was the case for Paragraphs 19 and 29. That being said, it should also be noted that the even though Paragraph 29 was deliberated in this way, it also gave rise to considerable controversy following the October 2000 revision of the Declaration of Helsinki. Certainly the introduction of a longer time period between the finalisation of a proposed form of its most important declarations and the final vote on these declarations in its General Assembly may avoid the turbulent and somewhat controversial process of adding a Note of Clarification.

4. There needs to be further thought given to whether the Declaration of Helsinki is essentially an aspirational document or whether it is a prescriptive document. Ruth Macklin raises this question without answering it: "Beyond these debates lies a deeper question about the nature of ethical guidelines. Should they be 'pragmatic' or 'aspirational'? Adherents of the view that statements such as the Declaration of Helsinki ... must be 'pragmatic' are likely to rely on current and past practices as a guide to what is possible. The pragmatists dismiss 'aspirational' guidelines as too lofty and, therefore, unrealistic. For their part, the 'aspirationists' tend to be reformers who judge past or current practices to be ethically insufficient to ensure that the highest standards for research apply everywhere..." (Macklin, 2004).

Philosopher Dorothy Emmet has considered in detail from several philosophical perspectives the value of what she terms a "regulative ideal": "To say that something is unrealisable is to speak with reference to a goal or standard which may be approached but which cannot be attained. Nevertheless, practice may be oriented towards it" [Emmet, 1994]. Essentially Emmet sees considerable value in the notion of setting out aspirational standards as giving a direction or orientation to practice.

With respect to the Declaration of Helsinki, the WMA seems not to have finally settled upon whether the guidelines are prescriptive or aspirational. The detail in Paragraph 13 (pertaining to the function of independent review committees and, as mentioned above, the longest and most complex paragraph in the DoH) suggests a prescriptiveness. On the other hand the far-reaching implications of paragraphs such as 19 and 30 have a more aspirational character.

At the same time the possibility that there is value in the ambiguity cannot be ruled out. The suggestion of prescription negates the aspirational nature of the guidelines being used as a convenient excuse for not fully meeting the apparent requirements. On the other hand, ascendance of aspiration over prescription means that research that is correctly oriented and moving in the "right direction", but not fully "there yet" will not be excluded.

4.6 Summary

In summary, I have traced very briefly the 1st to the 4th revisions of the Declaration of Helsinki. This set the stage for a detailed consideration of the process by which three of the most debated paragraphs of the fifth (Edinburgh, 2000) revision of the Declaration of Helsinki were formulated. In doing so, I described the relevant operating procedures of the WMA and then tracked the relevant portions of the proposed revision through these procedures. The aim of this exercise has been to illuminate further the process of "authorship" of the Declaration of Helsinki. To the extent that understanding the intent of the author is necessary in understanding the meaning of a text, it is hoped that this exercise provides additional insight into the potential ethical implications of the 5th revision of the Declaration of Helsinki.

4.7 Epilogue

This work, initially presented at an international conference, which took place in Hannover, Germany in October 2004, was eventually published as a book chapter in 2007. This author's contribution to that conference and subsequent writing-up of the presentation comprise chapter 8 of the book (Schmidt U & Frewer A (eds.). *History and Theory of Human Experimentation: The Declaration of Helsinki and Modern Medical Ethics*. Stuttgart: Franz Steiner Verlag, 2007) [Carlson *et al.*, 2007]

Details of how the WMA structure operates form an important part of this chapter and aid in the understanding of how, in particular, what can now be seen to be the most controversial paragraphs, i.e., 19, 29 and 30, came to take their final form in the 5th (Edinburgh, 2000) revision.

5. A TEXT IN THREE LANGUAGES

CHAPTER 5: A TEXT IN THREE LANGUAGES

5.1 Prologue

The World Medical Association (WMA) operates in three official languages: English, French and Spanish. Chapter 4 illustrated many of the internal workings of the WMA. All official meetings are conducted in these three languages with simultaneous (in as far as is possible) translation. It is possible, in addition, for individual National Medical Associations (NMAs) to fund their own simultaneous translations although the resource implications are considerable. For the Annual Assemblies observed by this author (Helsinki, 2003 and Tokyo, 2004) only the German and the Japanese delegations had arranged for simultaneous translations.

In analysing the paragraphs of the DoH, differences were initially noted between the English and French versions of the Declaration that on further reflection and discussion with a colleague more fluent in French suggested these may have significant effects on the interpretation of the text as well as in some instances throw light on how the English text might be interpreted. This of course gave rise to the question as to whether the same applied to the Spanish text.

What followed was the compilation of a team to ensure academic rigour – in particular to fill the gap in both fluency in Spanish and in linguistic theory. The team comprised this author, two additional medical colleagues, a professor of linguistics

and the two supervisors of this thesis. One of the additional medical colleagues had grownup speaking French and English and the other Spanish and English. Both of these colleagues have practiced medicine in contexts where both of their languages were needed. The senior academic, with expertise in linguistics, was needed to advise on the appropriateness of the chosen methodology. The following chapter (and a subsequently published paper) resulted. These show that there were both potentially important differences in meaning between the versions and, that in some cases, differences between the various language versions can help in understanding possible interpretations of the English version. The same may, of course, be true in French and Spanish but analyses using those languages as the basis for analysis would need to be conducted to prove this.

Appendix 6 shows the detailed paragraph-by-paragraph analysis of the text of the DoH across the three languages. It was through this that the particular differences that may be of significant semantic and ethical importance were selected. In addition, the text of the three "back-translations" can be found in this detailed analysis (see text of the chapter itself for an explanation of the role of these back-translations).

5.2 Introduction

One issue that has almost completely escaped mention in the debate on a global consensus on bioethical issues is the difficulty presented by linguistic barriers. Here I consider this issue in relation to the Declaration of Helsinki (DoH). This document has been central to the World Medical Association's (WMA's) efforts to achieve consensus on the ethical conduct of medical research and arguably remains the most important international document in this field. [Macklin, 2004; Lewis *et al.*, 2002]

Re-iterating the organisation's efforts, the Director of Ethics at the WMA, Dr. John Williams, has recently issued the challenge that "every effort should be made to internationalise bioethics" [Williams, 2004]. Indeed, the challenge of addressing differing ethical standards for research in different parts of the world formed one of the driving forces for the revision of the DoH in the first place [Macklin, 2004]. That these issues are still a flashpoint for controversy is amply illustrated in a review of the film version of John Le Carre's novel *The Constant Gardener*, written by Marcia Angell, whose 1997 editorial (in *The New England Journal of Medicine*) helped ignite the controversy [Angell, 2005]. The book and film portray the fictional nefarious actions of a multinational pharmaceutical company. However, Angell uses the opportunity of the review to state again her concerns that medical research standards may differ between countries, and in particular, that the standards of

protection for research subjects are lower in developing countries, and that some researchers continue to exploit these lower standards to conduct studies that would not be ethically permissible in the sponsoring country.

In its most controversial paragraphs (Paragraphs 29 and 30), the Declaration of Helsinki has sought to address aspects of this issue. The ensuing debate culminated first in the Note of Clarification to Paragraph 29 in 2002 and later in the Note of Clarification to Paragraph 30 in 2004.

Yet it also stands to reason that if international statements of ethical standards vary in their content across different language versions, this will be an additional impediment to the achievement of consistent international standards. I raise this question with respect to the DoH primarily because of the document's international prominence and its controversial attempts to go to the heart of these continuing ethical controversies. The DoH is relatively succinct at less than 2000 words (compare CIOMS at approximately 20,000 words)and exists in only 3 official languages (compare, for example, the European Union Clinical Trials Directive, which is much longer and must be translated into the 20 official languages of the European Union). Therefore the DoH is a less unwieldy starting point for this analysis.

The DoH exists in 3 official versions, one in each of the official languages of the WMA (English, French and Spanish) [WMA, 2004]. The WMA is the largest global grouping of medical professionals and currently numbers the National Medical Associations of more than 80 nations as its members [WMA, *Members List*, 2011]. Eventually, the DoH will be translated from the official versions into a multiplicity of different languages, and will then likely go on to influence the wording of many other documents, so internationally the stakes are high. The WMA gives no guidance on such further translation and it is up to the organisation that is arranging a translation as to which official version or versions to use as their baseline, and the accuracy of such further translations remains the responsibility of that individual or other organisation.

5.3 Methods

I undertook a detailed comparison (see Appendix 6) of the English, French and Spanish versions of the DoH. I was aided in compiling the catalogue of what appeared to be differences between the 3 versions by by doctors who grew up in contexts where they were fluent in both of the languages (NHG for the French-English comparison and LMP for the Spanish-English comparison) and who have used both of the relevant languages extensively in a professional context. To reduce the subjectivity involved in this process I obtained three translations of each of the

French and Spanish versions of the DoH into English. The translators were all language teachers and were not previously aware of the content of the DoH. These back-translations were used to verify the differences detected on initial analysis. The texts of these back-translations can be found in Appendix 6 within the analysis of each paragraph.

5.4 Results

A detailed comparison of the English, French and Spanish texts of the DoH reveals, not unexpectedly, many grammatical and stylistic differences between the versions. Although in many cases these changes were not dictated by rules of language syntax or any obvious aesthetic advantage, most differences did not affect meaning. For example, in Paragraph 5 the English and Spanish versions state, "In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society". The French version reverses the syntactic logic; "In medical research on human subjects, the interests of science and society should never take precedence over the well-being of the human subject".

The main concern of our discussion, however, is the small number of paragraphs where something important seems to be "lost in translation". Here I outline 5 that I consider of particular importance.

5.4.1 True opposites or a risky assumption? (Paragraph 1)

Table 5.1: The 3 official versions of second sentence of Paragraph 1		
English	French	Spanish
1. … Medical research involving human subjects includes research on identifiable human material or identifiable data.	1. … Celle-ci comprend également les etudes réalisées sur des données à caractère personnel ou des échantillons biologiques non anonymes	1. La investigación médica en seres humanos incluye la investigación del material humano o de información identificables.

The English and Spanish versions use "identifiable" whereas the French version states "non-anonymes" (non-anonymous) to define the kinds of studies using data or tissue samples that are covered by the DoH guidelines (Table 5.1). Ethical dimensions regarding protection of privacy of personal information in epidemiological and tissue sample studies have long been an issue for debate but the 2000 revision is the first occasion when the DoH has explicitly referred to such issues [Riis, 2000]. The question of an ethically relevant difference in meaning hinges around whether there is any difference between "non-anonymous" and "identifiable", or put another way, whether "identifiable" and "anonymous" are exact opposites of one another. Clearly, if the researchers know the identity of the research subject then data are "identifiable". On the other hand, if all possible re-linking of data with the person providing the data has been eliminated, then data are "anonymous". What about the intermediate situation where a code held by a third party separates the identity of an individual from the data used by the researcher?

These would seem to be "non-anonymous" in that if the right steps were taken, individual and data could be re-linked. But are they "identifiable"? Certainly they are not identifiable to the researchers and this may be considered to be the ethically important point. So we see that a grey area emerges that could possibly lead to different interpretations of the French version from the Spanish and English versions. Given that "non-anonymous" would be perfectly acceptable in the English version (and "no anónimo" in the Spanish), or that "identifiables" would be a valid adjective to use in the French version, I argue that this difference is unnecessary under the rules of the languages concerned and introduces an unnecessary risk of an ethically relevant difference in interpretation.

5.4.2 Whatever happened to "quality"? (Paragraph 6)

Table 5.2: The 3 official versions of 2nd sentence of Paragraph 6

English	French	Spanish
6. ...Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality	6. ...Les méthodes diagnostiques, thérapeutiques et de prévention, même les plus éprouvées, doivent constamment être remises en question par des recherches portant sur leur efficacité, leur efficience et leur accessibilité	6. ...Incluso, los mejores métodos preventivos, diagnósticos y terapéuticos disponibles deben ponerse a prueba continuamente a través de la investigación para que sean eficaces, efectivos, accesibles y de calidad.

Without explanation, the French version omits the word "quality" from the list of criteria by which medical methods should be evaluated (Table 5.2). This is of

particular concern because internal discussions subsequent to the adoption of the 2000 version of the DoH raised concerns that "safety" was not explicitly included in this list. It was concluded by the WMA's Medical Ethics Committee in May 2002 that "the aspect of safety is sufficiently addressed by the term 'quality', which is already mentioned in Paragraph 6" [WMA, 2002].

5.4.3 Three languages, three standards in the control arm? (Paragraph 29)

Table 5.3: The 3 official versions of the 1st sentence of Paragraph 29		
English	French	Spanish
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. …	29. Les avantages, les risques, les contraintes et l'efficacité d'une nouvelle méthode doivent être évalués par comparaison avec les meilleures méthodes diagnostiques, thérapeutiques ou de prévention en usage. …	29. Los posibles beneficios, riesgos, costos y eficacia de todo procedimiento nuevo deben ser evaluados mediante su comparación con los mejores métodos preventivos, diagnósticos y terapéuticos existentes. …

This paragraph (Table 5.3), along with Paragraph 30 (discussed below), has been one of the most controversial in the DoH. Both of these paragraphs, after lengthy word-by-word debate about their meaning, have had notes of clarification appended to them. In Paragraph 29, a major controversy relates to the appropriate standard of comparator in an active-control trial. Should it be the best available anywhere in the world or the best that was available to the population in which the trial was conducted [Macklin, 2004]? The change from "best current" (English) to "best

existing" ("mejores existentes" in Spanish) and "in use" ("en usage" in French) is arguably the most significant difference I discovered between the three versions. Although I recognise that there may be semantic overlap, the French "en usage" carries some implication of a localised availability. However, the 1996 French version used the word "courantes" ("current") in the paragraph dealing with placebo and the change to "en usage" paradoxically seems to move the translation further away in potential meaning. On the other hand, the Spanish version is suggestive of a universal standard of care for the control group. The debate over the standard of comparator arm is not fully resolved. In this paragraph, the difference between the three language versions illuminates the debate but, of course, does not resolve it.

5.4.4 Differing standards for use of placebo controls? (Note of Clarification to Paragraph 29)

Table 5.4: The 3 official versions of relevant portion of Note of Clarification to Paragraph 29

English	French	Spanish
...where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.	...lorsqu'une méthode prophylactique, diagnostique ou thérapeutique est mise à l'essai pour une affection bénigne et que la participation à l'essai n'expose pas à des risques supplémentaires de dommages significatifs ou durables.	...Cuando se prueba un método preventivo, diagnóstico o terapéutico para una enfermedad de menos importancia que no implique un riesgo adicional, efectos adversos graves o daño irreversible para los pacientes que reciben el placebo.

The English version, in the second of the two clauses defining acceptable conditions for the use of placebo where proven therapy exists, makes the requirement that there be no "additional risk of serious or irreversible harm" (Table 5.4). In the French version we find "des risques supplémentaires de dommages significatifs ou durables". "Durables", which translates most closely as "long-lasting", would seem to have a different meaning from "irreversible". The adjective "irréversible" is available in French or the English could be changed to "long-lasting" depending on what the intent is. The Spanish version uses "irreversible". However, the ethical demand does need clarifying. If a harmful outcome of a study potentially lasted several years (but was eventually reversible), would that really be acceptable? Our suggestion is that it would not and therefore that either the French version is preferable, or all 3 versions should refer to "long-lasting or irreversible" in this paragraph.

5.4.5 Requiring the impossible? (Paragraph 30)

Table 5.5: The 3 official versions of Paragraph 30

English	French	Spanish
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.	30. Tous les patients ayant participé à une étude doivent être assurés de bénéficier à son terme des moyens diagnostiques, thérapeutiques et de prévention dont l'étude aura montré la supériorité.	30. Al final de la investigación, todos los pacientes que participan en el estudio deben tener la certeza de que contarán con los mejores métodos preventivos, diagnósticos y terapéuticos probados y existentes, identificados por el estudio.

This paragraph (Table 5.5) has also been the subject of considerable controversy and, in October 2004, had a note of clarification appended. The English version calls for patients to be "assured of access" whereas the French requires that patients be "assured of benefit". This seems to be beyond what any ethical code can require. It is only the potential benefit (through assurance of access) that can be required. Perhaps a wording that combines the two versions could read "should be assured of access to the potential benefit of...". The note of clarification to Paragraph 30, added in 2004, may partially address this problem by speaking of "access" (accèss) rather than benefit, but the difficulty with the wording of the paragraph itself still stands.

5.4.6 "Must" or "should"?

Debate continues about whether normative ethical guidelines such as the DoH, which do not have the status of legal documents, are best seen as pragmatic (and thus able to be followed in every case) or as aspirational (thus setting the direction but recognising that not every case will achieve every aspiration). Interestingly, the versions may differ in this regard. This Spanish ("deber", and its conjugates, rather than the conditional "deberia") and French ("doivent" and its conjugate "doit" rather than "devrait") consistently use words more closely equating to "must". English, on the other hand, uses "should" 16 times and "must" 5 times where the Spanish "deber" and French "doit" are used. The one exception is Paragraph 4 of the DoH

where the English ("research … must rest in part on …") is translated in French as "peuvent imposer de recourir" (i.e., "may require recourse to …"). However, this sentence could be considered descriptive of a fact rather than a statement of an ethical guideline and thus is not a true exception to the statement above.

It is not possible simply by analysing the text to understand what to make of this, e.g., whether the Francophone or Hispanophone worlds see a set of normative ethics differently from the Anglophone world. Nor is it clear why the English version switches between "should" and "must". Further conjecture is therefore beyond the scope of this chapter. It remains, however, an intriguing difference that should be explored in further studies.

5.5 Discussion

Guidelines for WMA translations are not published. However, both Dr Delon Human, the Secretary-General of the WMA at the time of the revision, and Dr John Williams, the current Director of Ethics at the WMA, affirm that the translations should be as close as possible to one another, recognising that some differences may be imposed by the syntactical rules or the cultural framework of the languages (personal communications, 2004). Translation difficulties are an enormous communications challenge faced by any establishment dealing with people who

speak different languages and the WMA is no exception. Steiner asserts, "each human language maps the world differently" [Steiner, 1998]. To the extent that this is true, not only will the translations always contain differences, but also some differences will never be apparent to those trying to investigate them.

On the other hand, as Peter Kay has pointed out, cultural differences may be much more significant than linguistic differences and may lead to very different worldviews between speakers of the same language [Kay, 1996]. This is especially relevant in view of the worldwide distribution of the three official WMA languages: Spanish would be an important language for ethical discourse in settings as diverse as Madrid, Montevideo and Havana, French in Port-au-Prince, Paris and Montreal, and English in Glasgow, Gabarone and Auckland.

Some might argue that there is no empirical evidence for differing standards as a result of these translation issues within the DoH. I invite those who would contend this to consider both the difficulty in gathering such evidence (given linguistic difficulties), the long time-frame before those differences would be noticed empirically, and most importantly to consider whether we really want to find out about such systematic differences after the fact.

It was by no means the intention of this work to suggest that any of the three official languages should become dominant in determining the wording of the DoH or in any

other debate regarding issues of international importance in medical research ethics. One of the major drawbacks of this study is that analysis of the results has been in English only. Ultimately, in the absence of a universal language, there is no way around the fact that discussions of meaning must take place in one language or another. The use of English is dictated by the provenance of this work.

The existence of discrepancies that could lead to a difference in interpretation is worrying. That I have demonstrated the existence of such discrepancies in the case of the relatively succinct DoH across only three languages gives rise to questions about other key international documents that are longer and have many more official language versions. So what is to be done?

In the first instance, the WMA should address these differences either by way of explanation or by way of the necessary amendments to the DoH to harmonise their meaning. Given the intense word-by-word debate and analysis that occurs both in WMA meetings and in the subsequent literature about the DoH, attention to these differences between the three official versions is vital. The DoH remains too significant an international instrument to leave these inconsistencies unattended.

On a broader note, however, this study shows one possible source of variation in ethical practice regarding research in different parts of the world. It raises the much bigger question of how to detect and to act upon research standards that vary in

unacceptable ways in different geographical settings (I accept that some variations, e.g., greater emphasis on verbal consent than on written consent in different cultures, may be acceptable). One possible way forward was suggested by Dr Kgosi Letlape of South Africa, who held the presidency of the WMA in 2004-2005, when he made his speech as president-elect in Tokyo in October 2004. Dr Letlape mooted the creation of a surveillance unit to monitor coherence with the standards of research in various parts of the world. Unfortunately, this aspect of his speech was neither reported in the written summary [Anonymous, 2004], nor does it appear to have been taken any further by the WMA.

The last 50 years have seen the widespread recognition of two lines of defence for protection of people participating in research: voluntary participation through appropriate consent and the establishment of independent ethical review committees. What is lacking now, especially in the context of increasing multinational studies, is some system to ensure that standards worldwide do not fluctuate outside ethically acceptable parameters of variation. Dealing with the issue of linguistic harmonisation of ethical guidelines would ideally fit within the work of such a surveillance unit. However, harmonisation of the three official versions of the DoH need not, and should not, wait for its establishment.

5.6 Epilogue

The material presented above was published in the *Journal of Medical Ethics* 2007; 33: 545-548 under the title *The 3 Official Language Versions of the Declaration of Helsinki: What's Lost in Translation?*

6. HOW IS THE 5TH REVISION OF THE DECLARATION OF HELSINKI BEING INTERPRETED?

CHAPTER 6: HOW IS THE DECLARATION OF HELSINKI BEING INTERPRETED?

6.1 Introduction

What follows is the presentation of the empirical part of this work. Details can be found in the methodology section. Please note: this chapter is far longer than all of the others and is divided into separate subsections.

Although the Framework method has been in used for over 25 years, it remains one of the favoured methods for applied policy analysis – the type of qualitative analysis to which this study most lends itself (Ritchie & Spencer, 1994 pp.173-194 in Bryman & Burgess, 1994).

The framework for analysis was determined by the sampling frame for the project and by the choice of paragraphs in the Declaration of Helsinki (DoH) upon which the semi-structured interviews focused. The chapters already presented have, it is hoped, presented a strong case for the choice of the particular paragraphs. However, the a posteriori phenomena upon which this analysis is constructed was the observation of overt interpretive phenomena with respect to the text of the DoH that occurred during the course of the interviews as is explained further below.

In this section, the outcome of the semi-structured interviews is described and analysed with respect to any passage of transcript where an interpretive process is taking place. This can be overt – i.e., the word "interpretation" (or any semantically related words, e.g., interpret, interpretive) is used in the interview. In other cases it may be implied by the content of the passage. One prominent example of this, to which this discussion will first turn, is where the nature of the document, i.e., whether it is to be regarded as aspirational or prescriptive, is discussed.

6.2 Methodology

A series of semi-structured interviews were conducted. The foci of the questions were the paragraphs in the Declaration that on initial analysis appeared to represent the largest and potentially most contentious changes.

Each interview was structured with the aim of lasting one hour. While a small number finished earlier than this, many went well over the time. Most of the interviews were face-to-face, 4 were conducted by telephone. Some occurred in challenging contexts, such as over breakfast at a conference or between conference sessions in fairly noisy environments. This is the nature of interviewing "experts" – they tend to decide the timing and context!

Each participant was presented with the text of the relevant paragraph of the DoH on a sheet of paper. Printed below it, where applicable, was the text in the 1996 version.

They were asked for their opinion of the change and the likely impact of the change. From there, they were allowed to speak and occasionally prompted with a question usually along the lines of "Some have said [...] – would you have a view on that?"

6.2.1 The structure of the sample

Interviewees broadly fell into one of three groups with respect to their expertise and potential involvement with the development of the text of the Declaration of Helsinki or with the DoH's impact on the conduct of medical research:

1. Authors

These were people somehow involved in the process of drafting, debating and approving the text of the Declaration of Helsinki. By and large they were WMA staff or elected position-holders, or representatives of a national medical association.

2. Medical Researchers (MR)

This group represented those somehow directly involved in the medical research endeavour. There were representatives of 3 international pharmaceutical companies, medical publishing, funding bodies, health technology evaluation agencies, academic pharmacologists and drug-regulatory agencies . A total of 21 interviewees fell within this category.

3. Commentators

This group represented people who were in a position to make expert comment on the text of the Declaration of Helsinki but were not in any position of direct influence on the text itself. There was a broad spectrum of opinion on the part of the various interviewees chosen by virtue of their expertise in another relevant discipline. By way of the reminder, the disciplines represented in this group are: philosophy, medical ethics, law and medical jurisprudence and medical history. Many of these interviewees fall into more than one category of expertise (such as law + philosophy) or are medically qualified in addition to their other academic qualification. The inclusion of interviewees in this group does not imply that they have never participated in the medical research enterprise – it indicates that such involvement was not the primary purpose for which they were asked to participate.

6.2.2 Method of Analysis

The Framework method of analysis was used (see above). Interview data was coded and analysed using NVivo software.

Sampling Process and Analysis for Interviews

The sampling process had two main facets. It was (1) purposive; and (2) a snowball sample; explained as follows.

Purposiveness

Unlike the random sampling process for quantitive research, where the sample of a population is drawn with an intention of statistical inference to the entire population, qualitative sampling is often described as "purposive". There is a deliberate attempt to draw upon as wide a range of relevant viewpoints as possible. Purposive sampling deliberately chooses to sample individuals to give as wide a relevant variation as is indicated by the proposed research.

In the case of this study, a survey of as broad a base of stakeholders in both the medical research endeavour and among those involved in the drafting and interpretation of the Declaration of Helsinki was considered desirable. Further, a sample from as wide a geographical base as possible, within the limitation of resource constraints, was also sought. The division into the 3 groupings of "Authors", "Researchers" and "Expert Commentators" was something that emerged during the course of the conduct of research. It was not an initial part of the purposive sampling but perhaps could be considered an inevitable outcome of it.

Snowball Sampling

In snowball sampling, further research subjects are drawn upon based on the suggestions made by, or the contacts facilitated by, earlier subjects in the research. In

this study, early participants were asked whether they could specifically suggest any further research participants or generally suggest classes of research participants. Where logistical consideration permitted, these suggestions were followed up.

In total, the number of interviews was; 15 were "authors", 21 "medical researchers" and 21 "expert commentators". A full list of interviewees is available in Appendix 5. The specific interviewees are not identified as the results are presented. Rather they are coded and the results presented according to which of the above three groups they represent. Thus each quotation below is attributed to, say, A7, MR12 or EC11 corresponding to the "author" coded number 7, "medical researcher" coded number 12 and "expert commentator" coded number 11 and so forth.

The sample size was predominantly determined by the "purposive" aspect of the sampling method. It was determined, in discussion with supervisors and with Dr. McHaffie that the sample should attempt to include, if possible, all of the core group of "3 wise women" involved in authorship as well as the then Secretary-General of the WMA. Additionally the group of "medical researchers" should include representatives of the following (preferably two or more if possible from each): pharmaceutical industry, academic pharmacology, drug-regulatory agencies, research-funding bodies, medical publishers and treatment evaluation agencies (such as the National Institute for Clinical Excellence (NICE) in the United Kingdom). The group of "expert commentators" should include at least one (preferably two or more, if possible) from each of the following academic disciplines: medical law and jurisprudence, philosophy, medical ethics and medical history. By the time the above

criteria were fulfilled, the sample size of 57 had been achieved. Fifteen were from the authorship group and 21 each were in the groups of "medical researchers" and "expert commentators". The difference in size between groups is relatively small and because the world-wide pool of those involved in the authorship of the text of the DoH is less than that of the other two groups, it is not unexpected that this forms the smallest group. The schedule of the interviews is shown in Table 6.1 below:

Table 6.1: INTERVIEW SCHEDULE	
MONTH	INTERVIEWS CONDUCTED WITH:
August 2002	MR1; MR4; MR13; MR15; MR17; MR18; MR21; EC2
September 2002	A12; EC5
October 2002	
November 2002	MR10
December 2002	
January 2003	EC17
February 2003	EC9; EC14
March 2003	
April 2003	MR9; EC19
May 2003	A15; MR2
June 2003	A2; A4; A9; MR5; MR7; MR8; EC13
July 2003	A6
August 2003	C3; C20; C21
September 2003	A1; A3; A5; A8; A10; A11; MR3; MR11; EC8; EC10; EC12; EC15
October 2003	MR14; MR16; MR20; EC1; EC4; EC7; EC16
November 2003	EC18
December 2003	A13; MR12; MR19; EC11
January 2004	A7; MR6; EC6
February 2004	A14

As mentioned, no specific methodology has been developed to specifically analyse results of the type of interview conducted for this research. The Declaration of Helsinki (DoH) is specifically a code of ethical guidelines. Arguably the closest type of document to the DoH could be described as outlines of policy. The methodological approach that seems most suitable, therefore, for making sense of the results of the semi-structured interviews is that termed the "Framework" approach. As Ritchie and Spencer (1994) point out: "'Framework', the analytic approach described in this chapter ... was initiated in a specialised qualitative research unit based within an independent social research unit ... [and] the institute's work can be broadly classified as applied policy research".

Ritchie and Spencer identify 5 key stages to qualitative analysis as follows:

Familiarisation

Identifying a thematic framework

Indexing

Charting

Mapping and interpretation

However, Ritchie and Spencer also allow for a modification of the Framework methodology to be "guided by the original research questions to be addressed, and by the themes and associations which have emerged from the data themselves" [Ritchie & Spencer, 1994]. With respect to this particular study, stages 4 and 5 (Charting and Mapping & Interpretation) show considerable overlap and will be described together.

The stages of the application of "Framework", as applied to the data collection in this study can be characterised as follows:

Familiarisation: I conducted and transcribed all 57 of the semi-structured interviews. This was followed by a detailed coding process involving reading and re-reading each of the interviews. The interviews themselves followed this approach: after first greeting and thanking the interviewee they were asked for any general comments and observations about the 5th revision of the Declaration of Helsinki. It is important to bear in mind the timing of the interviews and the fact that all of the interviews took place after the addition of the Note of Clarification to Paragraph 29 and before the addition of the Note of Clarification to Paragraph 30. The interview schedule itself is presented below as Table 6.1. However, the discussion of the wording of the Note of Clarification to Paragraph 30 was ongoing at the time of all of these interviews.

Following this introduction, each interview proceeded through a series of questions relating to the major changes that had occurred in the 5th (Edinburgh, 2000) revision and which have been discussed extensively in the preceding chapters. These are:

Paragraph 29 and its accompanying Note of Clarification (Standard of control arm and use of placebo controls)

Paragraph 30 (Access to treatment at conclusion of study)

Paragraph 19 (Benefit to populations)

Paragraph 27 (Publication of research)

Paragraph 1 (Relating to identifiable tissue and data)

Paragraph 9 (Authority of the Declaration of Helsinki)

Paragraph 6 (Requirement to undertake research & associated 4 criteria)

Revised Structure of Declaration of Helsinki

Opportunity for comment on any other paragraphs as interviewee sees fit

Recommendations regarding interviewees (snowball sampling – see below)

Opportunity for personal reflection

Two of the last three components formed an important part of the validation process. The opportunity to comment on other paragraphs sought to confirm that the specific paragraphs chosen as the focus of the interviews was appropriate. Finally the opportunity for personal reflection (described further below) allowed for further understanding of the responses if any particularly idiosyncratic views were expressed. No particular paragraph in addition to the ones chosen was identified by any more than 2 of the interviewees as being important and the majority of interviewees agreed that the most important paragraphs had been identified. Although interesting, none of the statements made in the "Personal Reflection" part of the interview gave any additional cause for concern that the expressed views were so uncharacteristic of the broader medical research community that the data from that particular interview needed to be considered separately rather than grouped with the rest. The structure of the interview described above leads to the development of

the *a priori* codes shown in Table 6.2 (below). Further description of the coding process, in particular relating to the *a posteriori* codes, can be seen below in the discussion of the phase of "Indexing".

Table 6.2: Major Codes Used in Analysing Interviews
I. "A priori" Codes (determined by the structure of the interview)
Introductory Remarks Paragraph 29 Paragraph 30 Paragraph 19 Paragraph 27 Paragraph 1 Paragraph 9 Paragraph 6 Restructuring of Document Personal Reflections
II. Major "a posterior codes" developed as interview transcripts were coded (Presented alphabetically)
Authority of DoH Benefit to Population Clinical Trials Criticism of the DoH Developing Countries Ethics Committees Historical Insights **Interpretation (this was the most frequently used a posteriori code and deemed the most important for framing the analysis of the data)** Ongoing Access to Treatment Pharmaceutical Industry Philosophical Observations Positive Opinion of the DoH Useful Quotations

Identifying a Thematic Framework: The main thematic framework identified for this particular study is related to the division of the interviewees into the three major

categories described above: author, medical researcher and expert commentator and to the main paragraphs. Results for each of the paragraphs focused upon were analysed in detail to see whether interpretation was proceeding differently amongst interviewees drawn from the 3 major categories.

Indexing: as outlined by Ritchie & Spencer, "'indexing' refers to the process whereby the thematic framework or index is systematically applied to the data in its textual form". This was accomplished in this study by coding the transcripts of the interviews. This took place by a detailed reading of the interview transcripts and using the coding function available in the NVivo (version 2.0) software. Table 6.2 below shows the most important codes. These are divided into two categories: *a priori* and *a posteriori*. The *a priori* codes, as described above, indicate what segment of the semi-structured interview was being conducted at the time (e.g., Introductory statement, Paragraph 30, Restructuring of document, Personal reflections – as mentioned above). The *a posteriori* codes were those that emerged as a result of analysis of what was said by the interviewees. Some of the codes were used a great deal more frequently than others. Other codes were used very infrequently but the passages thus coded were left with these codes in case later interviews repeated those themes. Approximately 200 codes resulted in total. The full list of codes applied is presented in Appendix 7. Thus, after having coded the data above using NVivo, the transcript data was able to be divided into large continuous blocks of transcript (based on the *a priori* codes) which tended to be

sequential through the interview although sometimes interviews would go back and forth between the different paragraphs or would combine discussion of two paragraphs). The material coded under the *a posteriori* codes was, of course, scattered throughout the interview transcripts but could be brought together for the varying analyses using the NVivo software. After examination of all of the codes applied to the transcripts, it was decided in consultation with my supervisors that clearly the most important material was that coded under the *a posteriori* code of "**Interpretation**" (see Table 6.2). This code was both the most frequently used and the most voluminous (in terms of the amount of text coded) of all the *a posteriori* codes. More importantly, it reflected the central theme of this part of the thesis – how is the text being interpreted by a broad spectrum of those involved in the medical research enterprise.

This material coded under "**Interpretation**"was therefore studied intensely for patterns in the data as described more thoroughly below under Steps 4 and 5: Charting, Mapping and Interpretation.

At this point, it is useful to describe further how the above steps were validated using further triangulation processes. After approximately the first 10 interviews had been conducted. Dr Hazel McHaffie, an experienced qualitative researcher who had assisted in the construction of the semi-structured interviews selected 2 interview transcripts and reviewed the coding. She was able to confirm that the coding of these interviews was appropriate. The major additional point she made was to use a code for the passages that appeared to be potentially useful as quotations

to particularly clearly illustrate the material that was emerging. Thus at her suggestion the code "Useful quotations" was added to the list, the already conducted interviews were re-read and this code applied where appropriate. This category, as Table 6.2 shows, became one of the major codes used.

A further triangulation process was carried out later in the analytic process, once it was decided that the material coded "**Interpretation**" should be the central focus of the analysis. Three interview transcripts were chosen at random by one of the supervisors of this thesis (Professor Kenneth Boyd). This represented one transcript from each of the 3 major groups of interviewees. Professor Boyd reviewed the coding of each of the transcripts and confirmed that all of the material coded as "Interpretation" represented bona fide instances of such interpretation. The transcripts of the 3 interviews chosen for this exercise are presented in Appendix 8.

Charting, Mapping and Interpretation: Ritchie and Spencer (1994) go on to describe the 4th step of the "Framework" process (Charting) as follows: "Having applied the thematic framework to individual transcripts, the analyst needs to build up a picture of the data as whole, by considering the range of attitudes and experience for each issue or theme". Thus the material coded under "Interpretation" was sorted into the 3 major categories of interviewees and cross-referenced to the other major codes to see what differences in interpretive process may be occurring between the 3 groups.

Major interpretive patterns were identified as the coding proceeded and these are presented in the results section below. As an example, various interpretations of the term "benefit to population" were beginning to emerge and closer analysis led to the understanding related to the "strong" and the "weak" definitions of the term that are discussed in the appropriate section below.

In many respects the boundaries between phase 4 (charting) and phase 5 (mapping and interpretation) are indistinct in this particular study. The discussion in the results section (below) aims to represent a coherent equilibrium between these two phases.

Before moving on to the results section, potential sources of bias and the epistemological limitations of a study such as this need to be considered. The first, and arguably the most important, is my own subjective influence on both the interview and the interpretation process. In section 2.6 (above), I describe to the best of my ability how I would have answer the question in the interview relating to Personal Reflection, i.e., how I have come to hold the views expressed. Additionally, of course, my own perspectives and understanding inevitably changed with each interview I conducted. Part of the advice I received from Dr. McHaffie was to build this overtly into subsequent interviews. I frequently found myself following her suggestion to introduce such questions with the phrase "some have said..." to indicate earlier interpretations of the text by previous interviewees.

A further important source of bias is the time factor. It is, of course, impossible to conduct the interviews in a study such as this simultaneously.

Therefore the body of interview data has to represent an unfolding "work-in-progress" occurring alongside other events. In regard to the text of the DoH, the most important concurrent event was the debate regarding the addition of a Note of Clarification to Paragraph 30. Some of the interviewees (from all 3 groups of interviewees) were directly involved in this debate and others were not. Other interviewees had ceased involvement with the debate after the finalisation of the text of the 5th (Edinburgh, 2000) revision. However, the nature of the interviewees ongoing involvement (or otherwise) usually emerged in the General Comments section at the beginning of the interview and a further safeguards in the interpretation of the interview data was the inclusion of the final question on Personal Reflections. Finally, an important source of bias that should be recognised stems from the relative paucity of representation of major parts of the developing world in the processes and procedures of the WMA. It can be seen from Appendix 5 that most of the interviewees are from the developed world. The maldistribution of medical research resources has been well-described in Ruth Macklin's book "*Double Standards in Medical Research*" to which reference is made in the opening statement of the results section. A similar study to the one represented in this thesis, but focusing on interviewees from the developed world would be very likely to be extremely valuable. It was, however, beyond the resources available for this research in both time and funding.

So as I turn to the results section, it is worth pointing-out that it can be seen that the format represents the "matrix" created by the "thematic framework" and

"indexing" (in particular, the *a priori* codes). Each of the paragraphs on which this thesis focuses has the material coded as overt **Interpretation** analysed under the category of interviewee (author, medical research or expert commentator). In each of the "cells" of this matrix, the process of charting, mapping and interpretation of the data is presented and continued in the summary and analysis sections. It is perhaps fortuitous that Ritchie and Spencer (1994) have used the word "mapping". That is the metaphor which has been used to drive the primary question being asked in this thesis. It is worth at this point revisiting what was first stated in the abstract of this thesis: This detailed analysis of the text of the 5th revision leads to the central thesis question: "Is the DoH providing adequate guidance as a set of normative ethical standards across the broad spectrum of those involved in the global medical research endeavour as evidenced by reasonable coherence of their interpretations of the DoH?' Or, on the other hand, are the interpretations so diverse that the DoH cannot be considered a source of clear guidance. Or, put another way and incorporating the symbolism inherent in the title of this thesis: 'Does the DoH function adequately to map the 'landscape' of medical research"? It is hoped that the material which follows goes at least some way toward useful answers to these questions.

6.3 Results

6.3.1 The "genre" of the Declaration of Helsinki

Ruth Macklin explicitly addresses the question with respect to ethical guidelines in general in a section within *Double Standards in Medical Research* [Macklin, 2004] and her assertions will be summarised here. She first suggests that aspiration implies "impossibly ideal". This is in contrast to "pragmatic" – a term that implies that "the guidelines are truly usable in the practical world". However, there is another axis that may be important in considering the genre of the DoH. Is it intended to be "descriptive" or "prescriptive"? In the former, the guidelines describe standards that are usually adhered to in practice. However, given that a set of normative guidelines is, by definition, describing what *ought* to be the case, her view is that "descriptive" is not an appropriate way of interpreting the document.

Interpretation of any writing, be it poetry, legislation, the script of a play or any other form, is so thoroughly influenced by the genre of the document that this issue will be discussed first. It should be clarified that the use of the term "genre" here relates not to literary form in general, but specifically to the question of the intention of the authors of the DoH (and the interpretation of the nature of the DoH by medical researchers and expert commentators) In this context, the primary question relating

to the genre of Declaration of Helsinki is whether the document is pragmatic or aspirational in nature. If prescriptive, then the expectation would be that the letter of the DoH is adhered to in every situation and that where it is not adhered to, it can be assumed that the researchers' behaviour has fallen short in some way of the ethical standards set forth by the World Medical Association.

This leaves the argument regarding "genre" or "intention" with 3 important and somewhat distinct possibilities: prescriptive (always to be adhered to), pragmatic (practical and so generally able to be adhered to unless better ethical reasons can be offered for an exception than can be offered for adherence) or aspirational (they define the ethical direction researchers should face but recognise that in the current practical state of medical research, it is impossible to meet the standards on every – or arguably, any – occasion). How were these options reflected in the empirical data generated by the interviews?

Authors

The interpretative process with respect to the genre of the document was most strongly in favour of an aspirational status among those involved in the drafting of the DoH. Some observations occurred in the context of discussing specific paragraphs and related primarily to the paragraph concerned. Firstly, comments relating to the document as a whole are considered.

One of the authors (A6) asserted that there was a deliberate vagueness in the document to leave room for ethics committees to contribute to situation-specific interpretation. In response to efforts to transform the DoH to a much more detailed document the following was observed:

A6: ...We decided in the ethics committee [WMA ethics committees] at the time that wasn't the way we were going. ... They are general principles and each of those principles needs interpretation. ... and the safeguard from the patient's point-of-view are the ethics committees ... independent review committees.

When challenged on the fact that ethics committees themselves might look to the DoH for guidance thus introducing a circularity the response was:

A6: ...well it's a circularity in human nature isn't it and it's important there is circularity because we cannot be prescriptive in everything but it's got to be interpreted in the light of that guideline...

Another comment reflecting the genre of the document as a whole was along similar lines:

A13: ... one of the difficulties of the Declaration of Helsinki the more you try to nail down every last word and every last syllable the more difficulty you get into.

A third also backs up the "aspirational" nature with the reflection that there perhaps should be additional documents that are more prescriptive in nature but that the DoH itself should not follow this aspirational path:

A7: This is broad brushstroke aspirational lines. Whether it's World Medical, CIOMS, or national legislation, there in fact are literally thousands of issues that this touches upon. And some of them deserve their own paper that says 'touched

upon here' and' here it is in some depth'. Some of them deserve a more legislative perspective: guidelines, regulations, this is how thou shalt do it.

In perhaps the clearest assertion of the genre of the Declaration and the implications of its aspirational nature, the following comment was made:

A9: the Declaration is an aspirational document. It's not as if all of these guidelines can be achieved but that we are encouraging those in research to always reach higher and make sure that they do their research at the ethical level. That's what's in keeping with the medical profession's view on medical ethics that you would, you know that there would always be those who would not adhere to ethical principles but that would not distract us. We would still encourage all to go for the highest possible level of care and ethical practice.

One of those involved in authorship drew on a comparison with the Ten Commandments! Although not all might agree that this analogy is apt, it nevertheless represents an interesting insight into the thought of one of those involved in authorship:

A2: ...we know that it's very very hard to follow all the Ten Commandments especially when we read or hear that only a thought of breaking one of those is sin but it doesn't mean that we would change the Ten Commandments because they are so difficult to achieve. So it's an idealistic goal. This is something you would try to achieve and improve your conduct for the better.

Another alluded to the aspirational nature of the document as the reason it was decided by the WMA to abandon any attempt to compile a glossary of the meaning of the difficult-to-interpret words and phrases such as "best current" or "reasonable likelihood" (see below). By providing a glossary and thus tightening the intended meaning of such phrases, the DoH would be attempting to achieve a "paralegal status" (A4)

In conjunction with that observation:

A4: And that's really where we've come down to now in terms of the problems since 2000 around interpretation because it's not clear whether this is meant to be a didactic set of absolute rules or whether it is a set of guiding principles which people have to interpret sensibly and sensitively. And it seems to me that every time we debate it we go through the same hurdles ...

Further elaborating to make a statement that should also be recalled when considering Paragraphs 30 and 19 (see below):

A4: I think our view would be that it's a set of guiding principles to be interpreted sensitively and sensibly. That it's quite clear from it that the whole aim behind it is to protect individuals from exploitation. So that when you read clauses that are about the treatment that should be available at the end of a research protocol and best possible treatment, it's about discouraging people from experimenting in countries where people will have no access to care once the research trial is over. But that doesn't mean that you absolutely have to guarantee everything that might be available in the most heavily financed country in the world. But it does mean that you have to think about this, write it into your research protocol and see if the local research ethics committee think it's adequate. But again it's about the patient being at the centre, or the research subject being at the centre.

In all, 7 of the 15 interviewed on the basis of their authorial statements mentioned the genre of the document in some way as "aspirational". None of the "authors" had an opinion to the contrary.

Finally an interesting point: Although the following question could give rise to substantial debate, it is not a major focus of this study but gives rise to very interesting questions about whether the DoH is too paternalistic in its approach to protecting patients. As will be seen below, some of the authors do see a degree of paternalism as permeating the document. For example:

A6: ... the whole foundation of this Helsinki may seem a little bit patronising. It seeks to protect the patient not to protect doctors.

Medical Researchers

A very interesting change takes place when considering those interviewed on the basis of their direct roles as "Medical Researchers" in that there was very little direct consideration of the genre of the document in the process of interpreting the DoH. Only two directly addressed the "aspiration vs pragmatism" question.

One of the comments was critical of the absence of recognition in the DoH that pragmatism may need to enter the decision-making process with respect to research:

MR12: ... there has to be a balance between, if you like, what might be the pure ethical approach and something that's at least recognising there has to be some pragmatism.

It is interesting to follow further the comments of the same interviewee further and in the context of the discussion of post-research duty-of-care, the following observation was made:

MR12: ... that is – let's be open about this declare what the plan is in the protocol, that's not to say that if someone feels they can justify it, that the plan may still say "we run the study and there's minimal continuity thereafter".

RC: You'd have to get that through the ethics committee and get consent in that context.

MR12: Yes, exactly. So I think this is rather poor wording that's actually trying to reach or might be trying to reach an endpoint which I think we would have no problem with.

Even if the issue of "poor wording" is set aside for the moment, this reflects an interesting interpretive attitude with regard to the DoH. By recognising a valid "endpoint", an element of the aspirational nature of the DoH is implicitly recognised. Although it is recognised that not every study may achieve the aspirational goal, there isrecognition of the value of the goal articulated by the aspiration.

The only other "Medical Researcher" interviewee that expressed a view on genre simply posed the question as to whether the DoH should aspire to be a guideline document or a manual for practice.

Far more typical of the responses of those classified as "Medical Researchers" was to call upon an example, in many cases to illustrate what they considered to be flaws in the document – such as particular situations where the DoH is either difficult to interpret or impractical to adhere to.

And while the following comment does not relate specifically to the genre of the document, the words of another of the medical researchers illustrate clearly the interpretive challenges faced – and perhaps the difficulty in applying an "aspirational" document in practice:

MR17: ... reading ... um... the Declaration ... the interpretation is very difficult ... ummm ... because I think it's a job in itself to, and you are doing that, to really go in deep and what does it really mean in day to day practice. And just reading it it's most of the things sound really straightforward but if you look in day to day life on what to do it's, I think it's really open for debate it's not ... um ... a document where you can say well you can't do this and you should do that – it doesn't, it gives

guidance but at a very high level, and I think that's ... it is often not really clear what, according to the Declaration, is ethical to do and what's not.

Another of the medical researchers interviewed also raised the question of how detailed a document such as the DoH should be, suggesting that a brief statement of guidelines – allowing room for judgment – was a useful document:

MR6: Should it be [a guide to ethical principles or a manual chapter]? Personally I think that it depends on how ... how the Declaration of Helsinki – do we want to develop it into a guidebook or a manual chapter or do we want to stick with the principles. I mean we get criticised our regulations it's not specific enough. When you go back to talk to the drafter of the regulations, they will say "we need to have room to make a judgment".

RC: Case-by-case?

MR6: Yeah.

One further observation, admittedly on the fringe of the question of the genre of the documents was raised by the following medical researcher:

MR14: So as I read the document it doesn't necessarily hit me that it's a doctors' document as opposed to a patients' document. But then I haven't really read it with that question in my mind.

Expert Commentators

When the question of the genre (aspirational, pragmatic or prescriptive - "descriptive" has already been ruled out) came up among those selected for interview as "Expert Commentator", opinion appeared very much divided. Six of the

21 interviewees directly commented on the importance of the genre of the document in its interpretation.

In one case (EC10) the interpretation and application of the DoH was compared with constitutional judges "*trying to make a document play out in the spirit in which it was intended without asking for every 'i' and every 't' to be dotted and crossed*". This seemed to imply a latitude for interpretation of the DoH but not any latitude for adherence in that a constitutional judge ruling any legal instrument such as legislation or regulation to be "unconstitutional" would have that legal instrument struck down and rendered inapplicable. If this were the case, the "genre" of the DoH would have to be considered prescriptive (insofar as it cannot be violated) albeit with a considerable degree of flexibility as to how it was interpreted.

One of the "Expert Commentators", in the summing up and personal reflections portion of the interview (see the section above on interview structure) conducted a fairly detailed analysis – mentioning at the start of the comment that the placebo issue was prompting this reflection. The analysis is reproduced in full:

EC9: ...as to this placebo issue. I think I have just been impressed in some of the highly polarised debates on a few of the trials that have taken place, that absolute rules don't reflect the realities of many circumstances and I guess I came to be a pragmatist and say that we need principles but we also need, in many cases, to be stated in terms of presumptions and arguments that have to be made and debated and that process is very important. ...I tend to be open to the notion that a good process is a very important thing and that there are lots of times when one won't have absolute principles that determine things and it's really a matter of being able

to rely on something which is open to examination and requires justification and reasoning and allows input from people who are affected and that's one of the reasons why I think it's so important, particularly vis-à-vis the recognition that countries can, for good reasons, if they have a process which is adequately protective of their population, be willing to go ahead with research that would be unacceptable in another country because of different circumstances and that does not mean either that the first country is either doing a wrong or necessarily the victim of somebody else's exploitation. They can be self-governing and self-directing and have reasons which are reflective of the interests of their population.

If this commentator's opinion is the case, then a number of significant consequences emerge for the interpretation of the DoH. The first is an acceptance that a globally applicable prescriptive document is unachievable. Secondly, any aspirational document has to be so flexibly interpretable that aspiration and pragmatism actually blend into one another through what is termed "process".

This issue of the importance of process is carried forward by another of the "Expert Commentators" but in a slightly different respect. EC21 sees the primary ethical value of documents such as the DoH embedded in the process by which "every 5 or 10 years" the guidelines are re-visited by those from "all quarters of the globe" and questions are asked as to whether the guidelines need to be re-visited. The full quotation is, again, instructive:

EC21: The more you see the document as something that's not intended to have legal force but is intended as an assertion of principles, in my view, the crisper you should be. It may be necessary to encrust a code with interpretations. It does bind and there is a real need for consistency of interpretation. As a set of guidelines I think there is much to be said for leaving guidelines to speak for themselves and be it once every 5 years, be it once every 10 years, assembling the collective vision of what this might mean from the different quarters of the world and seeing if we need to change the guideline.

Another of the "Expert Commentators" was very highly critical of a set of guidelines that was intended as "aspirational" in nature. The comment was made in the context of Paragraph 30 regarding post-trial access to care but the implications of the statement go far beyond:

EC6: ... you should never have an aspirational document ... what this does is you put in standards that no-one follows: all the researchers who take the time to read it say 'no-one I know is following article 30 and yet they're doing their work, they're getting it published in the journals that said they wouldn't publish things that are not in compliance with Helsinki. Very clear no-one's taking this seriously. Now I'll look over the rest of the document and see which other articles I like or don't like to apply to this research'. Aspirations should always be in your commentaries, your footnotes, your preambles but the guidelines themselves should say 'here's what we expect you to do today. And we hope to do better in the future'.

This view could be seen as immensely critical of the 5th (Edinburgh, 2000) revision of the DoH in two major regards:

1. It is clearly being seen by those with an authorship function as primarily aspirational and therefore in this commentator's view the opposite of what guidelines should be;

2. The two later appended Notes of Clarification (to Paragraph 29 in 2002 and to Paragraph 30 in 2004) do exactly the opposite of what, if this commentator's mention of 'footnotes' and 'preambles' can be taken to be comparable, they should have done. The guidelines should state clearly what is expected in all cases. Footnotes and preambles (and Notes of Clarification if they can be considered to fall into this category) in this case explain the conditions under which exceptions to the aspirational guidelines can be considered.

Two other Expert Commentators reflected that the DoH tended not to be at the "top of the pile" when ethics committees were making specific decisions. It tended to be in the background – a guiding document for decision-makers. EC21 likened it to anti-discrimination legislation. This interviewee's assertion was that such legislation does not eliminate racism, ageism, sexism or any other forms of prejudice at which it aims. However, it sets the direction and in this regard must be seen as "aspirational". EC16 likened the DoH to human rights legislation and came to largely the same conclusion.

Another of the expert commentators, in summing up the opinions given in the interview made a useful statement about the genre of the document – again drawing a comparison with human rights statements and a contrast with the International Committee on Harmonisation's *Good Clinical Practice* guidelines:

EC5: I think that the context of interpretation's everything. Um ... I think that you have to try and establish what's the context of interpretation of the Declaration of ... both intellectual and I've suggested that you could ... you can take it as part of international human rights law. Some countries have taken it that way and implemented it as national legislation. Many others haven't. They don't see it as a legal statement at all but a guideline, an ethical ideal and that's really tricky to try and sort out. And also practical – who's using it? Where are they using it? Where are they required to use it? Who's checking up that they're using it? ... in the aftermath of the 2000 Declaration it was noted that the GCP doesn't require you to follow the Declaration of Helsinki, it requires you to design your research in accordance with the principles of the Helsinki Declaration which gives you quite a free hand in fact. If you take each article as a statement of a principle, you could be saying that you have to follow it letter and spirit. If you say that it embodies certain principles of good research practice and they are attempts to state some of them, then there's a principle and there's its statement and you can just look for the principle, concentrate the spirit of the Declaration, ignore the letter, if the letter is

inconvenient. Um ... so in the relationship between Helsinki and GCP, and in the end, GCP wins because GCP is international regulatory law and therefore it has economic clout. Uh ... and pharma spend enormous amounts of money and time, checking up, making sure that their studies are following GCP because it's about licensing and access to markets. Helsinki has no such status or leverage. It is .. it's a kind of motherhood and apple pie. Or it was until about 1998. It's since seen to be controversial and difficult. But until that point it was 'but of course we all believe in it. We all sign off on it. That's because we we're nice people not because our licensing depends on us auditing it, checking it up, making sure we're doing ...'. That's that's my view.

It is interesting to note, additionally, the strong statement: "I think the context of interpretation's everything".

In this discussion, the imperative is to bring together an analysis of the text – the DoH – and the variety of interpretations applied to it, with a reasoned argument about the ethical dimensions of medical research involving human subjects. The latter is a massive subject and impossible to cover in 10 theses let alone one. The focus of this discussion always leads back to the text of the DoH and what effect it is having on the view of the landscape of medical research ethics taken by those who, in some way, have a stake in the text. However, from time-to-time, it is important to stop and recognise that, in the final analysis this is not a closed discussion incorporating only the text of the DoH but it always opens out onto the broader issues of ethical discourse. This is well highlighted by the following commentator's observation – juxtaposing as it does the two major concerns at hand:

EC10: Because again I think that the complexities of ethics are not that something is either ethical or unethical ... it's not the dark of night and the bright sunlight. There are shades of what's ethical and sometimes by constructing your argument better

you can push it towards being more ethical. And ethical doesn't mean supererogation either. So it's how far you push it down that line. So I think the moral reasoning process is central to understanding whether something is ethical or not. It can't all be covered, I think, by sound bites in a Declaration. Again, I see Declarations as largely being constitutions that need to be interpreted. ... And that requires often a wise set of constitutional judges to interpret the constitution. It's not something that everybody can do off the hoof intelligently. And I'm not suggesting that interpretation should allow double standards but it should allow a consideration of the overall context, the scientific question, what the design is about, how much harm, how much benefit's going to be done, what the trade-offs are, the extent to which it's feasible to do the study to benefit that particular population. I think all of those things have to weigh into the moral argument in order not to just be guided by sound bites and simplistic statements.

This hearkens back to the notion of virtue ethics, or an agent-centred approach to ethics. A requirement for this "wise set of judges" appeals to an agent-centred ethical discourse, which is the defining feature of virtue ethics as opposed to the act-centred schools of deontological and consequentialist reasoning. This is hinted at but not decisively determined. It raises, however, a crucial point in this entire study – that of virtuous interpretation. As is often the case, a virtue is a middle ground between two extremes. Courage, as a virtue, lies between the vices of cowardice and reckless foolhardiness. Where might virtuous interpretation lie? At this point it may seem reasonable to suggest that virtuous interpretation lies between the vices of "disingenuous interpretation" and "pedantic (or overly literal) interpretation". At the same time, however, we must recognise a danger to the text at this point. The danger is a form of laziness or perhaps even a form of unjustified surrender (possibly a form of cowardice?). This laziness is a pause in the quest for the best words engendered not by a realistic appraisal of the impossibility of the task but by weariness; an

acceptance of a form of words because of weariness at the debate. One of the commentators summed this up as the "tired civil servant syndrome":

EC5: Um.... Yeah.... Good question. There is the um... tired civil servant of the Declaration which is that when Declarations are drafted there are core articles which everyone spends a lot of time on and then it gets closer and closer and closer to the cut-off, the civil servants stay up later and later and get less and less sleep, and their eye gets off the ball, and some things get put in which aren't really worked out in detail. I think there's quite a lot to be said for this as a theory of declaration-writing.

These words were spoken in the context of a discussion of Paragraph 1 and the reasons why the DoH may not have made any mentioned of "anonymised" research. Yet they have a procedural applicability far beyond that immediate context.

A comment by one of the expert commentators in the context of Paragraph 19 also has relevance in the discussion of the overall genre of the document:

EC8: Any sort of principles has to leave something open because you don't have principles you have something else – you've got rules or procedures. And I think the way it's addressed in [various codes of research ethics] ... are too weak because they've got all these loopholes – they let the [independent review committee] decide anything and it's just ridiculous – but leaving that part aside they do use other kinds of words like "every effort should be made" and "prior negotiations should take place" – now that would be a good step. To say ... to add another sentence and say that there should be prior negotiations among the researchers, relevant governmental authorities, international agencies if they are involved and the researchers themselves in making a reasonable plan for making products available after research. I mean that would not lock people in any way. But it would require that they demonstrate in some way that there have been these prior agreements.

This same commentator, in the context of discussing Paragraph 1 and the broadening of the scope of the Declaration made a further comment that is germane to the genre

of the DoH overall:

EC8: Well, there's a lot more missing on the storage of material. I would want to look again at the informed consent which I think is the lengthiest paragraph in the entire ... with the most detail in the entire Declaration ... to see what it says about all of these sub-categories specifically with regard to informed consent for stored samples for future research where you don't know what the nature of that research will be and whether it requires separate consent or whether it's part of the overall consent for the research. What happens to left over specimens from ordinary clinical care ... I mean there's a whole lot of details that are missing from this. But the Declaration of Helsinki would be a different document if it included the level of detail and all the amended detail that would be required to spell out all these varied circumstances.

Another of the expert commentators, in a stark criticism of the DoH, suggests an internal contradiction between what the DoH is purporting to do and what the text actually says. This comment occurs in the context of discussion of placebo-controls but it is readily seen the implications go far beyond Paragraph 29. Further discussion of this commentator's specific concerns about Paragraph 29 + NoC29 are documented later under the discussion of placebo-controls. The general statement is reproduced here:

EC13: Well I think you'd have to recast the whole Declaration to satisfy me. Because it seems to me that we should stop pretending that what this is, is what the World Medical Association would have you believe it is. I mean it is really a code of practice to encourage research, I think, rather than actually being a definitive defence of the individual against the hideous mobs of science. And I think there's a number of reasons for that. One I think quite innocently is that I think everybody if you ask, will say that medical research is a wonderful thing by and large and they want it to go ahead. But I think there's a less innocent outcome of Declarations like this one, in that they seduce the public into believing that there's a protection but in fact it doesn't offer the level of protection that I think individuals think they necessarily have. So from my point-of-view, if there's an interesting treatment which is reasonably successful, the interests of science in doing the kind of dramatic tests,

which would be the difference between placebo and new treatment, is only ethically able to be justified if the Declaration is up front to start with about what the principles it is that are actually guiding it. So if they are actually saying this is not really about protecting individuals pure and simple, it's really a code that ... it's designed to ensure that the best possible research can be done, there are then certain boundaries that don't actually abuse people in the way that the Nazis did. But that what we are doing is making assumptions. I mean I think it's a very utilitarian Declaration in that sense. So if you wanted to justify it in those terms I think you could. I mean if the best way to find out the most dramatic answer quickest is to test placebo versus a new treatment, then you could certainly build justifications for that by saying that it's in the interests of society that medicine can do these things because it means that they won't be going on for so long, you won't have to use so many patients, you know all sorts of things, so that there's a genuine possibly communitarian value in making that giant step rather than the slow progression that research often has to make when they can't use placebos. But that means the Declaration of Helsinki's a different thing from what it publicises itself as being. That wouldn't worry me because I already think it's a different thing. It would just be being honest about it. And it would mean, but it would mean that at least in theory an informed population globally could make a decision about whether or not that's right. You know, which is the more important value. So yeah, I think you can make a case for using placebos very often so long as you don't actually care about that instant group but that your ultimate motivation is to make dramatic leaps quickly.

In the context of a comment regarding Paragraph 27, an interesting exchange took place that applies to the interpretation of the entire document as a statement of human rights and the implications of considering the DoH to be such a statement. This comment emerged spontaneously about Paragraph 9 but alluded also to the final sentence in Paragraph 27 relating to proscription of publication of research not conducted in keeping with the requirements of the DoH. That sentence had not been a focus of the interviews because it had not changed with the 5th (Edinburgh, 2000) revision. However, the value of the spontaneous observation for the interpretation of

the entire document should be recognised. The implications of this will also be mentioned in the discussion of Paragraph 9 (see below):

EC16: ... you see if you look at it purely from a legal point-of-view people will say 'well national... strictly ... the law is the law in the jurisdiction and that's it'.

RC: Sorry what was that Latin quote?

EC16: ... that's a nice Latin phrase "that's the end of the question". ... In the case of ... but in fact anybody who approaches it from the human rights law point-of-view and I think one has to approach this from the human rights law point-of-view would say 'no it's perfectly appropriate to an international human rights instrument to say that we don't care what your classic jurisdiction says on this matter. This is overarching'. And that's to be expected in a human rights document. This is a human rights document. Because if you look at any of the ... say something like the United Nations Convention on the Rights of the Child is perhaps an illustration. It would purport to give children rights quite independently of anything which is setting it out and all that ... because these are aspirational documents. So that doesn't worry me at all. Although there is always going to be a problem because national law may be inadequate. I'll give you an example. Some local, ethical, national ethics committees would license procedures performed on a cadaver without consent of the family or pre-mortem consent and I know one case where it was involving resuscitation then airway research and the Austrian ethical committee approved of that.

RC: On cadavers?

EC16: Mmmhmm. On the grounds that they were testing a particular device without the consent of the family. And the view was taken by the journal to which that was submitted that this was unethical. So there is a rather interesting issue about what you do about something which is thought to be ethical in jurisdiction x, where it's gone through procedural requirements, but where you are sitting in jurisdiction y and somebody comes along and says that the ethics committee's approved this etc. and I think that you'd have to adhere to what you regard as ...

RC: Well certainly one that we've looked at already; it's interesting in the context that you say this is an aspirational document and yet it states that if research is not conducted in accordance with the requirements of this document that it should not be accepted for publication. And yet in an aspirational document it isn't recognised that many things are not yet achievable?

EC16: Um...

RC: And is it therefore ...

EC16: Maybe I shouldn't use the word aspirational now. No it's not. It's more prescriptive than aspirational. It sets out a standard ... a set of standards to which you should aspire so it's aspirational in that sense ...

RC: And many have used that word... but I'm just questioning ... is there a contradiction within the document? That on the one hand it's aspirational but on the other it's prescriptive.

EC16: What you are saying is this is what you should do ... this is what you've got to work towards and this is what you ... you must do this.

RC: Right okay.

EC16: And a human rights document would say that. A human rights document ... and you've got to see it as a human rights document. A human rights document wouldn't say "well you can continue to torture people but try to avoid it".

RC: Try to find other ways of getting what you want. Well thank you that's extremely valuable, comparing it to other human rights documents ...

EC16: And indeed, it's interesting to see that the Council of Europe convention puts human rights first as does the Convention on Human Rights in Biomedicine and UNESCO's international ... Universal Declaration on the Human Genome is human rights as well.

In this view, the commentator challenges the notion that many other interviewees had, i.e., that the "aspirational" and "prescriptive" could be, in any way, seen as opposite ends of a spectrum. They inextricably blend into one another.

6.3.1.1 Summary

Therefore to sum up we see 3 very different approaches to the question of "genre" in relation to the DoH, and as the last quotation shows, an infinite possible number of

blends of them! Four possibilities had been mooted: descriptive, prescriptive, pragmatic and aspirational. Both Macklin's arguments and the observations of the interviewees (especially the last one EC6) rule out "descriptive" as the genre for the DoH.

There is evidence of a very different approach to the question of genre between the 3 classes of interviewees. Those chosen on the basis of their role in authorship, by and large, set forth their understanding of the DoH as an aspirational document. The wording is deliberately chosen with a degree of imprecision for this very reason and a good deal of interpretive flexibility is envisaged.

Those interviewed by virtue of their participation in some aspect of the medical research endeavour tended not to address the issue of genre. However, the frequency with which these interviewees raised specific situations where there would be difficulty adhering to the exact words of the DoH as they understand them suggest that they may view the document as "prescriptive" in its intent (even though many recognise that it does not have regulatory or legislative authority in and of itself).

Finally, those interviewed as "expert commentators" reflected a mixed view of the nature of the genre and do not side firmly with any of the three possibilities under consideration. In one particular case, the very notion of an aspirational document was decried – in this case because it was clearly not "descriptive" of actual conditions in the actual conduct of research.

An argument could be made that the analysis should end here. The importance of genre in the interpretation of any document is regarded as central. It might seem reasonable to conclude that, because the genre is not agreed, the DoH has therefore so far to go in bringing the various understanding of medical research ethics that analysis of more specific points of interpretation is fruitless.

This, however, would be amiss for three reasons. The first is the observation by many that the process of argument about the wording is extremely important – perhaps more important than the decision about the final wording. To end the analysis here would preclude further discussion and understanding of the process.

The second is that, to be useful as ethical guidance, it is not necessary that the DoH provide complete agreement among the various interpretations but that the parties tothe conversation come to see that the others' points-of-view have a serious claim to make on their thinking and behaviour.

The third reason is that the individual parts of any document can only be fully interpreted in the light of the entire document *and vice versa*. To stop now would be to fail in the second part of this. Indeed, as will be seen as the analysis progresses a failure to interpret some of the individual paragraphs in the light of the whole is a considerable source of divergence of interpretations in many cases. This concern was

so great that in the 2008 revision the WMA chose to explicitly state in the revised Paragraph 1 that the document "is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs".

6.3.2 Paragraph 29 (& Note of Clarification)

The paragraph pertaining to the use of the placebo control design is arguably, along with Paragraph 30 regarding post-trial duty-of-care, the most controversial of the paragraphs revision in the 5th (Edinburgh, 2000) revision of the DoH. As was shown in the commentary, its change from the 1996 version was minimal in relation to the amount of controversy it generated suggesting that significant change had been expected. The subsequent appending of a Note of Clarification was also, as discussed, unprecedented in the history of the DoH.

This section will be divided into two parts based on what emerged as the contentious points of interpretation. These are: (1) the use of placebo controls; (2) the standard of control arm in the absence of placebo controls. Issues related to both the paragraph itself and its Note of Clarification (NoC29) are intertwined in the following discussion. However, specific issues related to the Note of Clarification are subsequently addressed.

A further consideration regarding the issue of using placebo-controlled trials surrounds the requirement for placebo-controlled trials sometimes imposed by regulatory agencies – does this comprise a "compelling" reason?

MR17: the FDA, the regulatory bodies want to see placebo controlled trials and I have been thinking about this. It says where for compelling and scientifically sound methodological reasons, it's necessary to determine the efficacy or safety of a method. That's something different from regulatory reasons. This is purely scientific. Compelling and scientifically sound methodological reasons, so it's about the method; and can you interpret that as regulatory requirements? If a regulatory body requires a design that is different from what is mentioned here (sound of slight banging on table as points to article) in article 29, can you interpret that as a scientifically compelling reason? That's the question. I don't know. But it's a matter of how you ... what your interpretation is. And I'm not sure. I'm not sure That's a question mark. So I'm not uhh ... I didn't see any discussons in the literature about this but there should be.

This issue will be taken up again in the summary.

6.3.2.1 Paragraph 29 and placebo

Authors

Those involved in the authorship process again continued to reflect the aspirational nature of the DoH and the latitude they believe the document confers with respect to interpretation. One example of this is as follows:

A6: Now that interpretation is sometimes on a case-by-case basis and the safeguard from the patient's point-of-view are the ethics committees. ... That is the sort-of safeguard because you can never write a totally prescriptive document. Even the law allows a little bit of freedom under the law. ... So in each particular area we can't write a completely prescriptive document. And that was the position that the ethics committee [of the WMA] *... came to ...*

And this general statement – although spoken by the interviewee in the context of Paragraph 29 led to further interpretation of the paragraph itself:

A6: I mean the whole principle is that the risks should be minimal or small. Again, it's related to the condition you're treating. If the ... if the new drug offers great hope and of course, this raises the question of whether the patient then benefits as a result of the trial then people who take risks in that situation are happy to do that in order that at the end of the trial "well this is really effective and then I can have it". And they'll be prepared to take that risk with the benefits they may then perceive from the new medication. So it is a risk/benefit analysis and quite frankly it's not something that you could be precise about and the danger about having individual cases, you know, which is a fundamental way of case law in the UK, is they would be ... if you just had one or two, they would be extremely selective to try and make a comparison between. And I think if we went down that road, it'll be more difficult ... But if then you require a larger number of case laws, bottomless, and then you have to interpret the difference between them. And to some extent you'll be bouncing around the head of a pin if you're not careful.

Yet it is difficult to argue, as mentioned in the commentary, that the initial statement of Paragraph 29 allows for the sort of latitude in interpretation spoken of here.

A key element of contention in the NoC related to the Boolean operator between the two "exception" clauses appearing to concede situations where, despite the existence of proven active treatment, a placebo-controlled design may be used.

Interestingly, in this regard, the authors by and large defended the use of the word "or" – meaning, of course, that the satisfaction of either "activated" the exception clause.

A5: We want "or" – we do not want "and".

This same author, in response to the "or" versus "and" debate suggested not having a connector at all but that the debate be solved by removing a connector entirely and let the two passages speak individually for themselves.

This was stated bluntly and forcefully – emphasising that the scientific argument was "compelling" (i.e., in the strong sense in which "compelling" means "compulsory" rather than simply "convincing"). In the remainder of the response, the clear need for balancing risks and benefits was emphasised as was the need for case-by-case debate. For example:

A5: Then to what extent can we stop a drug for a diabetic? Or a hypertensive person? To what extent can we give her a placebo? That is the issue that we discuss. But we cannot say more. ... "if 29 is too rigid for some, and the clarification is too flexible for others, is there someplace in between where we need to be?" I don't think you throw out the Declaration, you simply realise in fact that you somehow find the appropriate moral, ethical guidance that is also liveable with in day-to-day function.

In this case the analysis had been prefaced by the very interesting observation:

A7: [the influence of the Declaration] isn't waning so much as we're clearly in a period of transition that says "you know ... did we miss the mark?" and you don't throw out the baby with the bathwater – you don't throw out the Declaration...

This author clearly saw a great deal of the value of the DoH in the discussion generated by its contentious points and even agreed specifically with the suggestion that discussion of the text was useful even in the absence of agreement regarding

what its content should be. This author confirms their earlier comment observed above that:

A7: I ... believe that 29, 2000 and that language in 1996 say the same thing: but, were I looking for an excuse to do placebo-controlled studies, I might like the previous somewhat less explicit language.

Another issue that was not touched on by very many of the authors in their interpretation of Paragraph 29 was that the placebo use, where proven effective treatment exists in communities where that treatment had not previously been available. The statement in the paragraph would clearly seem to preclude such a conclusion but one author was concerned that, if argued vigorously enough, the "scientifically compelling" clause in NoC29 could be used to justify this practice. The comments made are interesting, articulate and impassioned and the final passage of dialogue provides a very interesting analysis of how the practice of such research may be interpreted by the affected communities themselves. It also provides a compelling example of the difficulty in choosing the wording of a document like the DoH that strives to be global in its reach. This comment was made in the context of a discussion of trials of antiretrovirals to prevent vertical transmission of HIV.

A3: ... There's a 3rd person and this is the unborn baby and that baby is now being given the full exposure, the full risk when there are things that can be done to protect it. Now the argument that they use is to say "now what's the difference. This mother has no access to treatment anyway. So we're not doing anything. We're not altering the course of nature so to speak. And we will gather valuable scientific information".

RC: Plus you're going to benefit the treatment arm.

A3: Yes. Plus you know retrospectively you've found on loads of regimens that a single dose before delivery and some after delivery - it has an impact. And how many babies were not protected to get that information. Now go back to the Declaration of Helsinki. I guess in the mind of scientists and researchers that were researching on subjects whose dignity had been taken away, who were extremely vulnerable, were living in concentration camps. ... They were condemned anyway. And it's all the notion of the ... you can experiment on prisoners. And remember the Declaration, the pretext of the Declaration was Nuremberg. And the Declaration was a refinement.

RC: How do you respond to the people, you know, one of the scientific addresses from the developing countries where one of the justifications is that these communities want this research, they welcome the research.

A3: Well, the communities want treatment. Communities don't want research they want treatment. So what you are being presented with is a lie. The communities don't want to be subjects of experimentation, they want treatment. Now when communities don't have access to treatment, being subjects of experiments is now being used as a form of access to treatment.

A particular criticism levelled by one of the Expert Commentators (see the section below for full comment) was that the NoC29 was not a "clarification" but a "change" with respect to placebo requirements; a comment refuted by many in the authorship group including:

RC: Now a number of people have commented in different ways. One person was particularly dismayed that the note of clarification wasn't in fact a clarification but a modification, a change.

A4: I don't think anybody believed that. They believed that it was genuinely a clarification of what we were trying to say.

RC: Right, right.

A4: But you know I mean this is the problem you can interpret words in so many ways and remembering that it was written originally and was then translated or read by people for whom English isn't their first language that adds other confusions. I

mean we have had a lot of problems with the translations with the two other working language of the WMA. And people say when you say that in French there is no difference between that word and this word and it does cause difficulties. And that's why I say, it shouldn't be, you can't be absolutist about this. It is about sensitive interpretation of guiding principles. The principles are pretty strong in the sense the overwhelming principle is you should not do anything that puts your patient, you research subject, at risk, if it can possibly be avoided.

So, perhaps unsurprisingly, the authors defended the wording of the DoH and continued to stress the aspirational intentions behind the text.

Medical Researchers

In the case of many of the medical researchers interviewed, a key question surrounded what was meant by the word "proven". One particularly incisive view illustrates a key differentiation between "proven" and "available".

MR17: ...the last sentence [of the actual text of Paragraph 29 not NoC29). It does not exclude the use of placebo, so that gave room to us ..., or no treatment in studies where no proven prophylactic, diagnostic, therapeutic methods exist. ... And I think you can debate what the word proven means. Erm ... because is that the same as a registered drug for that indication, is that proven effective therapy? Maybe yes, maybe not. Another product that is in development with, for instance, another company, that has some positive phase III results – is that proven? Proven effective? Not sure. So it is the interpretation of the word proven. I guess what's also a question here, and I think that looking at the um ... the note, the additional note here, explaining erm... because I think the discussion was started based on what I said: the FDA, the regulatory bodies want to see placebo controlled trials and I have been thinking about this. It says where for compelling and scientifically sound methodological reasons, it's necessary to determine the efficacy or safety of a method. That's something different from regulatory reasons. This is purely scientific. Compelling and scientifically sound methodological reasons, so it's about the method; and can you interpret that as regulatory requirements? If a regulatory body requires a design that is different from what is mentioned here (sound of slight banging on table as points to article) in article 29, can you interpret that as a scientifically compelling reason? That's the question. I don't know. But it's a matter

of how you ... what your interpretation is. And I'm not sure. I'm not sure That's a question mark. So I'm not uhh ... I didn't see any discussons in the literature about this but there should be. But I think that's one of the main questions. Ummm ... when you ask people that put together this article would allow placebo-controlled trials if regulatory bodies require placebo-controlled trials in this type of patients? It's a grey area.

One key interpretive aspect contrasts the notion of "undertreatment" of some research subjects with the scientific need to "blind a trial". This is well-illustrated as follows:

MR5: ... But we also use placebos if we want to blind a trial of the new treatment against the old treatment and they don't look the same. And so I think one of the things that worried me a lot about this is that the concept of placebo which is purely a mechanism for blinding had got entangled and is still to an extent entangled with the concept of an undertreated control group.

This medical researcher went on to describe the "double-dummy" technique – the details of which are not the important feature here but then went on to strongly re-iterate:

MR5: ... And so that's a double-dummy technique and that's completely different from what is talked about here ... exclude the word "placebo" because it's not a no treatment and the two concepts have got very entangled because when people talk about a placebo-controlled trial they mean really a trial where the treatment group gets nothing.

This goes to the core of the ethical debate around the DoH and its mention of placebo. Comments and views such as this were germane to recommendations made for the 6th (Seoul, 2008) revision. In particular this, in the view of this author, underpinned the concern that placebo-controlled designs should not be singled out in

the DoH (see chapter 7). The general principle of assessing the foreseeable risks and benefits, and ensuring that these were ethically appropriately balanced, outweighs any consideration of the specific design of a study.

Further, it lends credence to the concern that two issues relating to placebo controls have become conflated. The first is the concern that research subjects, if randomised to a "no treatment" group, may be subject to undue risks. There seems only one ethically sensible reason why this should be considered a special case in the requirement to weigh foreseeable risks and benefits and that relates to the notion of "therapeutic misconception" – defined as an ongoing belief, despite an informed consent process taking place, that all aspects of a research study are conducted in the individual's best interests.. However, if this notion of "therapeutic misconception" is the reason for specifying placebo-controlled designs, then some mention should be made of that.

The other issue is the argument that a placebo may be justified in resource-poor populations because they wouldn't have had access to any active treatment anyway and so nothing that would be otherwise available is being withheld. This situation cannot be seen as anything except a double-edged sword – whichever way the argument swings it does damage. On the one hand, if the primary concern is not the population in which such a study is done is the population that stands to benefit most then it is difficult to come to any conclusion other than that population is being exploited. However, where the intervention is genuinely intended to benefit

primarily the population in which it is being trialled, and where there is a genuine state of equipoise as to whether the putative intervention is superior to placebo then it is difficult to see what is gained by closing the door completely on the notion of a placebo-controlled trial.

Others articulated the difficulty in having a clear policy statement with respect to the standard of comparator arm. MR16, for example, argues that such a policy statement (except in general terms "aim for the highest ethical standards") is impossible to construct and sees a case-by-case consideration as essential. The examples will be considered below when this study examines how the three groups of interviewees tended to use specific examples in their interpretive considerations.

Another of the medical researchers raised an interesting interpretive point that, admittedly, is at the margins of interpretation of NoC29, since it is specifically addressing placebo-controls. It is the question of the possible serious or irreversible harm that may arise from the prolonged use of medications where the evidence-base for their safety in long-term use is deficient:

MR14: Let me just read the ... so where prophylactic, diagnostic or therapeutic methods are being investigated for a minor condition I guess I suppose you could argue that for some people migraine is and the patients who receive the placebo will not be subject to any additional risk of serious or irreversible harm. You see that seems to me a bit difficult because the very fact that you're using this drug in a very early stage on people with this, you never quite know about whether there's going to be serious or irreversible harm there.

This means that the DoH seems to suggest that a "sin of omission", i.e., putting research subjects at risk by "withholding" treatment (i.e., randomising some to receive placebo or no treatment) is greater than a "sin of commission". This latter refers to the undocumented possible risks associated with continued usage in the absence of long-term safety data.

The following comment cropped up in the discussion about the standard of control arm and it is to this issue that the 1st sentence refers. However, the interviewee went on to make an important statement regarding the ethics of placebo use:

MR3: So I just wanted to say, that's the harder question. ***The one where you need the placebo to get the answer you need for your country, I think that's easy. And I think most people find it easy.***

RC: I take it from some of the comments you've made in this context, that a non-inferiority study of the A-II inhibitor versus ACE inhibitors would be so difficult and require so many patients ...

MR4: If it were informative, that would be okay too, but I think that would be very difficult. And one reason for that is there's been too much progress. The ACE inhibitor trials were done adding only to placebo. Since then everybody gets a beta-blocker, some people get spironolactone maybe. If you did a trial where you denied those therapies that would raise ... you know where those were available ... that would raise questions. I don't know what the effect of an ACE inhibitor is anymore, how big is it you now have people on a beta-blocker and spironolactone so it would be hard, very hard to do a non-inferiority study. You might have at one point but you couldn't now.

The underlined statement strongly suggests a view that placebo-controls are justified if the benefit of the study is to be applied in the country conducting the study. Of course, the issue of the placebo-controlled trials in vertical transmission of HIV studies is always lingering in any discussion of this.

Finally, another view from a medical researcher about the logical (or Boolean) connector "or" in NoC29:

MR19: Well I would be very happy about the 'or'. First of all because it's an endless debate about whether or not a condition is minor – yes or no. Things that we think are minor are not minor to the patient and so it will be an endless and useless debate. Secondly, my experience if you want to talk about that is in CNS, in psychiatry. And that is a situation where the disorder is subjective, the scales are subjective, everything is subjective and if we can't have a placebo there we will never get progress. It's almost impossible. And that's why we have published in this way.

This researcher strongly argues that "compelling scientific or methodological reasons" should be sufficient to permit placebo control even where an absence of increased risk of serious or irreversible harm cannot be demonstrated.

Finally, one of the medical researchers felt that Paragraph 29 + NoC29 were too prescriptive and that a more detailed account of expectations was necessary. Again, the transcript is reproduced as it is difficult to improve on the way the interviewee articulated the concerns:

RC: In what way, if you see this as too prescriptive, in what way might you change that? What would you like to see changed to make it less prescriptive?

MR7: Well, the clarification needs to be expanded to include a washout period, for instance, in many conditions. I think the term, what constitutes a "minor condition" I would maybe a condition with a long natural history where what constitutes a minor delay in treatment over a natural history of several years is not likely to lead to any harm. And whether one wants to quantify what they mean "likelihood of harm" that by an ethics committee that if you didn't give a patient with hypertension antihypertensives now, then the patient would have a stroke tomorrow. And therefore it was unethical to offer a placebo-controlled trial. So I guess ethics committees don't have it laid out for them what the natural history of a condition is. So

something expanding of that area there around minor condition or short-term use in a condition with a long natural history where the patient's unlikely to come to any serious harm. … As it's written there it implies it implies a condition that's self-limiting, which hypertension, for instance, obviously isn't. Not subject to any 'significant' additional risk of serious or irreversible harm, then there's an argument of what constitutes significant. And that we need to be perhaps laid out to the patient and let the patient decide whether they would accept the risk. I think that would be the major area I would look at changing. There's two areas – one around washout, and one around what constitutes minor condition – the interpretation of that.

Of course, the final sentence sums up the two particular interpretive concerns not adequately addressed, in this interviewee's views, by NoC29.

Expert Commentators

The following comment by an expert commentator sees NoC29 as helpful. Of note, however, is the observation "you can't actually cover everything in a simple statement" having already spoken of the difficulty in understanding what the term "compelling and scientifically sound methodological reason" means. This commentator's observations draw forth a major interpretive difficulty. Not everyone in a position to ethically evaluate proposed research will have the necessary "insight" (to use the word chosen by EC10) into the methodological issues to evaluate the case as to whether it is "compelling" or not. Taking this into account it might be seen as a deficiency in generality of the DoH.

EC10: The Note of Clarification: yeah, I think the Note of Clarification is helpful but I think there is some concern about compelling scientifically sound methodological reasons. It's not quite clear what that means. If it means a study can be done better because it's smaller, that's not a scientifically valid reason. If there's some reason of interpretability, that might be valid. But again, like many Declarations, it's not actually clear what that means. This is the kind of statement that Bob Temple for

example often makes, from the FDA, and he says you can't do the study scientifically you can't design it in a way that it's going to give you the answer unless you have the placebo. And that's a statement that I don't have insight into methodologically and so I would like to see the reasons spelled out in more detail. The other thing that I .... Is this question "will not be subject to any additional risk of serious or irreversible harm". I would say this has to be only minor. So, for example, I have no difficulty with using a placebo for studies on rhinitis, or the common cold. Or a mild analgesic for something transient. I have no difficulty with placebos there. But placebo for a life-threatening condition? Placebo for treating a serious disorder like schizophrenia? It's much more complicated and some of the literature on those subjects makes you realise that you can't actually cover everything in a simple statement ... broad, a general ... so I think the clarification is helpful but it shouldn't detract from what 29 is actually saying.

The appropriate Boolean connector was also taken up by the following commentator who points out that it may not be a simple decision between "or" and "and" because the nuanced meaning of "or" may be more than meets the eye:

RC: You also mentioned that you would take the plain meaning of this one as "or" meaning either one or the other...

EC18: Clearly it would seem to mean one or the other. At least ... it would appear to mean that at least one of these conditions must be satisfied. Possibly both but at least one. And that is not acceptable in my opinion. I think that the 2nd condition to do with any additional risk of serious or irreversible harm itself must always be there and so in fact I wouldn't have put it in terms of 2 bullet points, as it were, I would put it in terms of saying "It may be ethically acceptable provided ..." and then the 2nd one provided, much more like the old... the old statement which says "this does not exclude inert placebo in studies where no proven diagnostic or therapeutic method exists". Now it's even stronger – what we would be saying is that if you can show that this is a minor condition and there's no real prospect of harm you can then consider it but only if you can show good reasons for it. Otherwise, if we took only the 1st one you could have someone argue "well this may well do people... It does increase the risk of serious or irreversible harm but it is scientifically necessary". I can't imagine that can be right.

RC: Okay.

EC18: I must say I'm extremely unhappy with the whole note of clarification which I said earlier I think is an attempt to undercut completely the whole spirit of 29.

Further opinion from the commentators regarding "and" or "or" as the link between the two exception clauses regarding placebo sometimes elicited equivocation:

RC: Now it's been objected that the Boolean operator that sits there should be 'and', i.e., both of those conditions should have to be fulfilled before a placebo-controlled trial is ethically acceptable, not either/or.

EC11: Well I'm not so sure about that. I think that what ... I'm just reminding myself. I think the first arm is basically saying 'look is this good science or not?' Is that right?

RC: Yes.

EC11: The 2nd arm is saying, 'well if it's "or" it's saying 'if it's not good science, it doesn't really matter if the risks aren't too great". Well that's rubbish. And therefore it must be 'and'.

RC: This person's concern if the risks aren't too ... no sorry if it's scientifically compelling you can take whatever risks you like ... the risks could be risk of death through going into a placebo-controlled trial as long as someone can come up with a scientifically compelling reason. And their argument was 'no it should be both scientifically compelling AND of a minor nature in terms of the risk that the person is taking'.

EC11: Well it depends. No. I think that's getting silly because sometimes getting back to the example I used ... you have all sorts of situations in medical research where risks and even risks might be high without well as it were I mean we can talk about what high means but where risks are high and the science is good and under the circumstances, I mean given the lack of any particularly good therapy, available therapy it would make perfectly good sense to proceed. So I mean what ... you would never necessarily want to argue that you shouldn't proceed when the science is good and the risk is high, simply because the risks are high. Am I missing the point?

RC: No.

EC11: If that's so you seen then it gets back to what I've said several times: what is essential here is not trying to sort out these problems on a priori grounds. I mean the Helsinki Declaration already covers, prior to the revision, I mean you know in relation to, for example, is it good science (a) if it's not don't do it; or (b) is the risk/benefit ratio justifiable – if not, don't do it? Now who is going to decide that?...

But if it's going to be decided in an acceptable way it's got to be by an independent committee that's functioning as it should be. So yet again a lot of these issues to me revert back to the process of whether or not the review that's taking place is taking place in a rigorous and coherent and consistent way.

Another of the expert commentators spontaneously raised an interpretive issue relating to the question of the placebo and gives insight into international and cross-cultural viewpoints:

EC6: I was particularly taken by the fact that the man from [named Asian city and country] said "we refer to this Helsinki Declaration as ... or this placebo provision in the Declaration of Helsinki as the 'let them eat cake' provision". And I was amused that he used a Western metaphor to voice his Asian complaint. He said, "basically it say you can't have effective treatment unless you're wealthy".

The same commentator also voiced strong views regarding the argument about whether the logical connector in NoC29 should read "or" or "and":

RC: What do you think of that argument?

EC6: I think it's an inane argument. If you have something that will present no additional risk of harm, then you don't even need part (a), if the standard is no risk.

In a lengthy interpretive statement, another of the expert commentators was very critical of the DoH in respect of its position regarding placebo. The comments have broader interpretation implications generally and a general statement by this commentator has already been discussed under the "genre" discussion above:

EC13: ... Well this just sort of takes me back to my fundamental problems with the Declaration if you don't mind me talking about them yet again. It seems to me that ... in terms of language it doesn't actually look as if these two make ... there's a huge difference between them because in both they actually permit the use of placebo. One

of them is much ... the new one is much more positive about the use of placebo, I think, than the previous one. But at least in terms of language it doesn't look as if there's a huge difference but to me, because I'm suspicious about what the World Medical Association is doing and has been doing in its Declaration, I think the newer version is much more permissive of the kinds of research that would have been actually potentially criticised in ... or at least would have been open to much more scrutiny in the past. It's one of the problems with any kind of Declaration it seems to me is that when you start, when you get experience as to what's going on, and you have experience of what kind of things that people do who are going to be subject to this Declaration, that is, medical researchers and scientific researchers actually need or say they need in order to achieve a goal which everybody regards as being, in quotes, a good thing, that the temptation to deviate from relatively terse statements about what's do-able and what's not do-able into padding out the information that you have about what your researchers would like to be doing without, in my view, necessarily, really scrutinising the fundamental purpose of what you're because a lot of it's accepted or a lot of it's ... it's accepted by the scientific research community or it looks like a way forward to achieve a good thing and so rather than going back and asking and testing themselves against the original theoretical proposition that they were looking at they tend to sort of lose the tightness of the language and insert other permissibilities which, in the long run, may not be a dreadful thing. I mean it may be that the actual effect of this on researchers is very insignificant given that it's not ... I mean we're really just saying more or less the same thing but what we're doing is saying it in such a way that if you interpret, if you choose to interpret it in that way then it's very much more permissive by appearing to postulate that there are, in this case, 3 examples of situations in which, for example, use of a placebo is not excluded. There isn't, in my view, any more than a kind of pragmatic justification for it in the note of clarification. And there isn't an attempt to re-address the ethical issues and work out on what ethical foundations you would to be making those kinds of assertions. So it's like a, it's like a piece of legislation where you have a very terse sentence about something. And then you go to the explanatory note and it makes it completely different. So I mean I think, whether or not this makes a difference in my view will actually depend on whether the researchers spot the difference. And they arguably might not because it isn't really that significantly different in terms of its language.

Again, another view from one of the expert commentators illustrates two key points.

The first is the subtlety of clauses such as those appearing in NoC29. It is easy to

"read over" tiny words that are critical to the entire meaning of a portion of the text.

To what extent should the drafters of any document such as the DoH attempt to foresee these subtle differences and frame the document so that it becomes more difficult to read over them.

EC16: Yes, oh yes I see yes ... sorry I read right over that "or". Well, yes, that "or" is quite significant in that you could ... and I think that that really is ... that's really unfortunate because if you only have to satisfy the 2nd condition rather than the 2 conditions it's ... if you take the disjunctive view of that you could theoretically use a placebo in an investigation for a minor condition where you didn't actually have a good reason for doing the study in the 1st place so they can't have meant that. I think the "or" obviously the "or" seems to be a mistake. On the other hand, that conclusion that I've just reached about where if you didn't have scientifically sound methodological reasons for doing it would mean that the research would be unethical anyway so you know ... it wouldn't ...

As will be seen later in the consideration of the 6th (Seoul, 2008) revision of the DoH, the interplay of Boolean operators become more not less complex. In view of the above remark this represents a change that could be considered unfortunate and this will be taken up in more detail later.

The 2nd point of note in the above interpretation is its "reversal" of the usual order of concern. Those advocating the need to change "and" to "or" tend to stress the necessity that the 2nd clause (requiring no risk of serious or irreversible harm). They cite, as has been discussed, the possibility that "compelling" methodological reasoning could be used to justify research that risked such harms if the "or" were to stand. This commentator picked up the fact that if the 2nd clause were true but the 1st not, then it could lead to un-scientific (and thus, by definition unethical) research

designs. It effectively would be stating (again, arguably requiring that this passage be taken out of context of the rest of the DoH) that if there are no risks of serious or irreversible harm then the scientific adequacy of the proposed methodology can be ignored.

Finally, another of the commentators (EC7) felt, regarding NoC 29, that:

EC7: ...it's so broadly defined that it does become a let-out clause for some of those who wish to do a placebo-controlled trial even though they know the patient would be better off if they were having an active treatment by an active comparator.

The summary of these views will be left until the discussion of Paragraph 29 + NoC29 after the next section.

6.3.2.2 Paragraph 29 – Standard of control arm

Considerable interpretive debate went into the wording of the standard of control arm specified by the DoH. The eventual choice of words was that the appropriate comparator (where placebo was not used) was the "best current prophylactic, diagnostic and therapeutic methods". Understandably this gave rise to considerable discussion of the interpretation of the phrase "best current".

Authors

Perhaps the most succinct indication is the following exchange:

RC: Should the comparator arm be the best available in the world or the best available in context?

A6: Oh well this is extremely difficult isn't it?

This dialogue typifies the difficulty with interpretation of this aspect of Paragraph 29. Thesame interviewee went on to clarify:*A6: I think it depends in the context the trial is being taken. If the trial is specifically... the purpose of the trial is to do that very thing, so look at the best available and compare it then I think there's no question that has to be used. But the construct of the trial is important.*

The debate raged in many quarters and led the UK Nuffield Council to release its own guidelines at about the time these interviews were held. The Nuffield Council had recommended the minimum standard of control arm was that which was available through the public health system in the country concerned (Nuffield Council, 2002). Unfortunately, this did little to resolve the debate as evidenced by the following:

A15: It's still not how I see it. And I couldn't see how in a world document any kind of reference to a health care system was going to work because even the words "public health care system" mean different things in different places so they're a meaningless set of words as far as I'm concerned.

This same interviewee commented at another point:

A15: ... I always understood that this was one of the bits of text that was left unsaid because I would choose to interpret that as meaning ... "best" as meaning "best in context" ...

And to further emphasise this view, as well as to highlight the debate about interpretation of "best current" the following comment is illustrative:

A15: Right, so there maybe a better delivery modality. Let's take pain relief for example. You might say in a particular situation that the best proven, the best

available, current method of delivery in pain relief situations is to use syringe drivers and patient modulation. But that would be a technology which would simply be undeliverable in a situation in sub-Sarahan Africa. It would be undeliverable on a battlefield as well. Right? So pain relief is context specific. So if we have the patient in a hospice or a general care facility or an intensive care facility we can fit them with a syringe driver and let them control dose, we'll let them do it. But you know if we're talking about some guy in a trench somewhere or somebody in an [developing country] and the answer is a one-shot injection, that's what we'll use.

RC: Yes. So your understanding is that the ...

A15: I was prepared to interpret it that way. And I think the words let you interpret it that way. But you're absolutely right that there were people who wanted to use words to specifically ensure that the best meant the world best.

A very helpful response showing the debate as part of the authorship process came from an individual closely involved with the 5th (Edinburgh, 2000) revision:

A9: there was clear consensus in the Workgroup that this should be changed because it is very troublesome to use the word "best" there especially in any international context because what does 'best' mean? What does 'best' mean and secondly what is 'current'? Is it this year, this month, this day? And that we found problematic. But on going back to the different committees there was a huge backlash; almost an emotional flood saying that we could not change this. I remember some passionate speeches from some of our Brazilian colleagues, some of our German colleagues who said that there's more to the wording 'best current' than just what it stands for. And that if we were change it to anything else like for instance 'the highest attainable' and the different other options that we looked that that would water down the idealistic nature of this paragraph and of this guideline. And that, in a sense, is true because the Declaration is an aspirational document. It's not as if all of these guidelines can be achieved that we are encouraging those in research to always reach higher and make sure that they do their research at the ethical level. That's what's in keeping with the medical profession's view on medical ethics that you would, you know that there would always be those who would not adhere to ethical principles but that would not distract us. We would still encourage all to go for the highest possible level of care and ethical practice.

As might be reasonable to expect, the issue of standard of control arm – especially when considering this might imply "best in the world" - is at an extreme end of the "aspirational" side of the debate discussed above. This clearly applies the aspirational genre to the interpretation of this phrase in the context of Paragraph 29. Even the phrase "highest attainable" was insufficiently aspirational. The highest aspiration is to continue to better the world's knowledge and ability to prevent, diagnose and treat illness. However, the acceptance of this wording seems to be a clear acceptance that this paragraph in particular (and arguably, by extension, the DoH more generally) sees itself as at the extremes of aspirational in nature.

This is borne out even further by another observation and a plea for "reasonableness" in interpretation:

A4: Sure. Yes. But I mean, let's be reasonable. Everybody recognises that there are always internal variabilities and that you can't guarantee, you know nobody can be on the doorstep of the Mayo Clinic or its equivalent locally wherever you are in the world. But you can say the best available locally so that if you weren't in that trial and were getting the best local treatments it would be the equivalent of that. That must be the bottom line and a lot of people would like to push it higher and would say "if your public health system has said 'we will not offer the following drug' but that is the best treatment and that is the other arm of the trial then that should be available if there's good evidence on it". And there's continuing disagreement on that.

Another of the authors stressed the danger of trying to interpret the phrase "best current" in Paragraph 29 without taking into account other elements of the DoH:

A3: Well, the problem is ... that's the danger of picking something out from a document and focusing on it. You know the thing that journalists do they do a one

hour interview and they go and they pick up one sentence and everybody's asking because it's other countries. Now that's the danger of taking a particular paragraph and not understanding in terms of the whole document.

RC: Right right. Or even a particular phrase.

A3: Or even a particular phrase and not even the whole paragraph. In my opinion that's part of the problem because if you combine 29 with 19, you can then reasonably extrapolate what best treatment should mean.

This interviewee went on to explain what was meant by this, linking this phrase with the requirements of Paragraph 19 (reasonable likelihood of benefit) and Paragraph 30 about ongoing access to care. This not only helps with the interpretation of the phrase "best current" in Paragraph 29 but provides an excellent illustration of the principles of interpreting individual passages in the text in the context of the whole::

A3: Because it says don't do it if the communities can't benefit from the treatment. So the best treatment default would be what's available in that community. But you must also look on the flip side that what you're researching does that community have any reasonable chance of accessing that treatment? So the people can't be dogmatic, must look at it as a holistic document. ... Okay. Now if what I'm looking at works, I must make it available to the subjects ...

This is in reference to the requirements of Paragraph 30 but this interviewee discussed the three paragraphs (19, 29 and 30) in conjunction with one another:

A3: If it doesn't work, what's the default, the default should be to what the system was offering and it doesn't mean the obligation is on you okay. But those things must be clarified. Now you can't have a no treatment default. Okay. And that's where you get voluntary informed consent. You say to the patient 'this is what's available as a form of treatment in the system. This is what you have access to and that's what you will default to if it's necessary for a default'.

RC: And you can't default ...

A3: You can't default to no treatment. If you default to no treatment, you're violating 19 because you shouldn't even be considering research in those sites.

And this ties up the requirements of Paragraphs 19, 29 and 30 into an understanding of the combined effects of these three controversial paragraphs.

This difficulty in interpretation of "best current" and the linkage between the interpretation of Paragraphs 29 and 30 are well-illustrated in another author's comments:

A13: Well it's a difficulty that's common to Paragraph 30 as well. I mean Paragraph 30 talks about the "best proven prophylactic, diagnostic and therapeutic methods" and these are not absolutes in that a lot of the things you might hold up as best treatment would be arguable. There would be a series of treatments on offer, each with a string of pluses and minuses associated with them and often it's a value judgment as to which of these is the best and there may be and frequently is a situation where you don't put your hand on your heart and say "well that is the best proven method". I would ... maybe what one is talking about is acceptable methods of treatment. Now that begs a whole series of questions of its own but this to me encapsulates one of the difficulties of the Declaration of Helsinki the more you try to nail down every last word and every last syllable the more difficulty you get into.

Another of the authors expressed surprise at the controversy over the statement. However, the insights described formed an important part of the recommendations subsequently made for the 6th (Seoul, 2008) revision and so is mentioned here:

A11: I find it odd that this should be controversial. This I'd have thought had always been good practice. Mind you, we tended always to take the view that if we thought it was a good idea to carry out a clinical trial of any kind that we'd be entitled to do it so long as we could assure patients involved were volunteers. ... And we tended rather to assume that people would accept that we acted in good faith. But we didn't

always. And I can think of examples, very very serious examples, especially of younger academics whose main consideration was their personal advancement.

Finally, in what could perhaps be considered at view at odds with those expressed by any of the other authors, at least one favoured the interpretation that the standard of control arm for pharmaceutical trials was the best available in the world:

A14: I think we have to put it in the context of the nature of the trial under consideration. If it's a drug-related trial, it would be the most appropriate drug therapy ***that is known at the time*** [emphasis mine]

This is moderated somewhat by the comments of another of those involved in authorship:

A8: But today when we're talking about international studies, multi-centre studies then you cannot leave to the best practice in that country. So what I would say is it depends on the researcher. If the researcher is in the country it is just a local institution, be it the university or a hospital conducting a research then obviously he has to do it versus what he would be giving in any case. Whereas if we're discussing an international study with multi-centres then we are already looking for an international best practice. I just want to say that the guiding rule in my opinion that the patient should not or if not a patient then in any case the one who's participating in the research should not be worse off than he would have been without the research.

Another very key observation, given the context in which the debate took place and helps in understanding the thinking behind the text:

A10: ... the voices of the [developing countries] were heard and that carried very clearly into the debate at the 2000 assembly where [representative from developing country] and others argued very strongly that there shouldn't be any double standard, that this should mean the best current anywhere even though the ... um ... trials were taking place in very poor countries. And there it's true that the focus of the Declaration of Helsinki has been broadened to global ethics and this was an opportunity to do that and that was seized and it was basically agreed to at that time.

I think there were voices of resistance before but in the end it was accepted that way. And the note of clarification of course ... yeah we can get on to that, but that's what was happening at the time.

RC: So the 'best current' debate – your view of this was it actually envisaged 'best existing?'

A10: Yes. And the people who held that view and argued it very strongly said "that may not be the case now but that's the way it should be. And this should be an instrument for improving medical treatment in developing countries".

Medical Researchers

The group interviewed by virtue of their involvement with various facets of the medical research enterprise also struggled with interpretation of the DoH's stance on the appropriate standard of control arm. For example,

MR8: ... The subsequent version without the clarification and instead of saying best-proven used the words best-current and some people I think read more into "current" versus "proven" than might have ... might have actually been there. Again, best current does give one a bit of leeway of "best current where?"

How much hinges on the adjective "current" as opposed to "proven"? Certainly, one possible interpretation could regard "current" as "currently available". However, this does not necessarily restrict one to an interpretation of "currently available in context". Clearly, given the right combination of funding and international transport, whatever is "currently available" is some part of the world is, at least theoretically, available everywhere. However, it remains at least arguable that "best current" can more easily give rise to this contextual debate than "best proven". At one level, proof

is proof. If there is evidence for something being better than anything else (i.e., best) then, unless one has recourse to a bona fide argument that this may be the case in one population but not another on the grounds of response to treatment (for example a drug might be best proven in a population with a low prevalence of G6PD deficiency but an entirely different entity may represent "best proven" where the prevalence in the population is higher), then "best proven" is "best proven". It is an epistemological statement. There is a genuine knowledge claim about "best" based on "proof".

One question regarding interpretation of Paragraph 29 highlights an aspect of interpretation that suggests a narrowing of the understanding of the standard of control arm and to what the term "best current" refers. When it was suggested that "best current" might mean more than just "efficacy" (e.g., it could refer to side effect profile, which was the example used by one interviewee), the response suggested a narrower approach to the concept of "best current":

*MR12: .... generally when people put this point they mean if there's something else and you probably would wish to show yours was better, the first take is usually from an **efficacy** standpoint* [emphasis mine]

This is a fascinating point of interpretation since the phrase "best current", standing alone, does not appear to give guidance as to the frame of reference of the word "best". It is at least arguable that "best" could be taken to mean "best tolerated" or

even "cheapest that gives reasonable expectation of successful treatment" (that may be "best" from the point-of-view of allocation of health resources).

Further interpretation relating to the term "best current" and the standard of control arm illustrates some of the practical difficulties faced in trial design. It is worth bearing in mind that this comment came from the same researcher who made the strong plea for "pragmatism" and the need to take "practicalities" into account. However, this demonstrates the possible impact in excluding some communities from multicentre trials:

MR12: ... we end up quite often using a collection of different countries and then, of course, you get the problem being compounded because you have to, for study design purposes, you clearly want a common comparator, and so ... and sometimes you do have to adjust the mix of countries because you could have a situation where for various reasons there could be countries where they have the therapeutic experience and they have the investigators who would be well-able to do the study but for some reason the comparator you have available that is recognised as being relevant to most of the other countries hasn't yet made it onto their market. And so you sometimes have to say "yes we would like to have included your country, but since you don't have product X and we feel it's critical to this particular study, you can't participate".

Another comment by one of the medical researchers illuminates further some general points of interpretation:

MR15: Well I think that in answering this question I'll speak as a physician not as a clinical researcher. The point of ethics will be the point of the patient's welfare and I think that the ... in almost every field in medicine you will find pre-existing therapies. There are very few fields where there is one therapy that has been proven beyond doubt to be superior to the others. Obviously, if you have something that has been proven to be superior then you should use this as the standard. But all others ... if it's generally accepted by the medical community that's involved in this ... in this particularly ... the best in practice.

Analysis of this remark suggests a strict interpretation of Paragraph 29, i.e., the comparator arm should be what is regarded as "best in practice". However, this begs the question of the most appropriate way of deciding what is "best". This is where the "speak as a physician..." comment gives rise to some concern. It suggests a duality in how to weigh evidence and suggests that one standard might apply to physician *qua* physician and a different standard to *clinical researcher*. Yet how can this be the case in any rational epistemological set of principles for making knowledge claims in medical practice!

Expert Commentators

It is a simple concept but often requires profound thinking to articulate it – the "best current" has a multivocal aspect to it. What does "best" mean? A strictly scientific interpretation may lead to one conclusion. However, as the following commentator demonstrates, there is more to the interpretation of "best" than the scientific interpretation has to offer:

EC18: It would be well... we'll start there then. Yes, I think there are ambiguities in the phrase "the best current" apart from scientific uncertainties which ... in terms of whether one can ever say there is such a thing as the best rather than a series of options there is that side of it. But also, best in what sense? And if one puts in a social context, you can imagine a poor country in which what is best for them actually is not a very very highly expensive therapy that maybe we've trialled because they're never going to be able to afford it in any case and in that sense it's really pointless to talk about that as the best current. But then one has to ask the

question about whether it should be trialled in that country. I think we'll come to it later.

Somehow implicit in this description of "best" is the concept of "the way forward": "where to from here?" While an aspirational statement describes the destination – is it incumbent on a "pragmatic statement" to describe the route? And indeed, it should be noted, such a route is very seldom straightforward?

A further fascinating phenomenon of interpretation was demonstrated by one of the expert commentators. This interviewee repeatedly argued that the nuances of interpretation were not very important. Supporting this view was the description of the DoH as almost a literary work of art and claiming that the form of words was not the key benefit that the DoH brings to the ethical debate but that the debate engendered by revisions of the DoH was the greatest contribution of the document.

Consider for example the following views relating to the standard of control arm:

RC: The ... some of the debates of course, have centred around issues like "best current" and what does that mean? The comparator arm required to be the best current. Would you care to...

EC12: Best current, best proven, best available...

RC: Best existing?

EC12: Best existing ... there's all different ways to skin a cat I guess.

RC: And all are valid?

EC12: That's not the issue in 29 so who cares if they're valid or not?...

RC: Well, it is if you are using an active control and someone is saying "aha but you're not comparing this with the best current practice?"... Or they might be saying "why are you using the best current practice?"

EC12: No I agree I agree.

RC: ... when you're doing a study in Thailand, you know...

EC12: I agree I agree. Again I agree. People are talking about it. But it's not why they are talking about it, it's not the issue. The issue is the problem of methodology of medical research. That's what's behind 29. That's what the issue is. "Best current", "Best available", "best proven", doesn't change anything because the word "method" is so confused there that it's fantastic. It doesn't have to change.

RC: Okay

EC12: I don't care what you write there, really, I don't care – it won't change anything. I mean ... the importance of this document, the impact of this document is on the discussion. It's on the discussion.

This approach clearly has profound implications for the task of textual interpretation. Clearly the text, in an approach such as this, must have something to say to the questions of medical research ethics. If this were not the case, and the argument stretched to its logical conclusion then any text whatsoever, a passage from Shakespeare perhaps, could stand under the title "Declaration of Helsinki". So, presumably, the words cannot be nonsensical or completely off the topic. The conclusion appears to be, however, that even if the words are not optimum, the debate engendered by the search for words is a real medium for shared understandings among diverse views among the often vastly-different perspectives of those debating medical research ethics.

This particular commentator, in summing up, made the following observation that applies to the whole DoH but, because it relates so directly to the "interpretive methodology" this commentator applies, the statement is reproduced here:

EC12: No I think it's a ... I like ... Helsinki is a fantastic thing, it's fantastic. Even the mistakes are fantastic. You can ... you know like it says here the primary purpose is to improve therapeutic procedures and the understanding of ... well the logical order would be 'the primary purpose of research is to improve understanding and procedures ...' but if you really go back and think about it very often we improve our procedures before we improve our understanding so even ... every place where there is a confusion in Helsinki or a misunderstanding, what's really good about it is you can see that confusion, that misunderstanding or whatever reflected in the practice of research in the world. So more power to it.

A profound interpretive statement that, if true, implies a paradigm shift in our understanding of a document like the DoH. Effectively, it becomes an account of what is shifting in the thinking of the biomedical research world. The issues that change in the DoH provide an insight into the history of such shifts in thought but cannot be seen to be an authoritative guide to such thinking.

A further expert commentator describes the interpretation of the phrase "best current":

EC6: Yeah, here's an opportunity for exegesis. The term 'best proven' was introduced in the 1975 revision of the Helsinki document. ... in the CIOMS document, which I think is a far superior document, because it does not take matters like this into account. It's much longer. It makes clear that first that there is no such thing as a best current method. It's usually a collection of established effective interventions. And secondly, you can withhold these under certain specified circumstances; one of which is if there is no best proven or best current or established effective therapy that's available in the host country and your purpose is to develop something that will be of value in the host country. Then if you follow certain other criteria you can justify the trial.

And another commentator expressed views regarding "best current" pointing out the change from "best proven" [4th (Somerset West, 1996) revision] and questioning what may have been the thinking behind the change:

EC8: One little thought about the wording: the difference between Paragraph 29 and the former version, the previous version is this is best proven and they changed it only to best current. And I don't know the debate that went on there but I understand that there is and has been discussion that I've participated in and heard that says "well what does 'best proven' mean? Does it mean the result of a randomised clinical trial? Does it mean approved by a drug regulatory agency? Does it have to be proven in all countries?" I mean there are lots of questions about proven. I don't know how that played out in the WMA in its words.

This commentator went on to point out difficulties with the use of the word "best" in any such phraseology – contrasting words chosen for CIOMS and other documents pertaining to normative ethics in medical research:

EH8: ... And he argued, and I think correctly, and I accepted his view that an "established effective treatment" is better [wording] than "best current". Because the trouble with the word 'best' is it means someone's got to debate and discuss what is best. And suppose they got one standard of care in UK and suppose they have something else in the United States for whatever it is. And then you get into an endless debate about whether our method is better than your method. Knowing that in developing countries ... in developed sorry, in industrialised countries there may be different modalities all of which are accepted and acceptable in the individual country, not a poor developing country, the words established effective don't require you to come up with the best and then be shot down by somebody who says it's not best. So that was another – I think a slight shortcoming ...

Another of the commentators, although not spontaneously addressing the definition of "best current", when prompted made some insightful interpretive remarks:

RC: The last question regarding Paragraph 29 I'd like to ask is: some have raised issue over interpretation of the words "best current" in saying that a new treatment

or prophylactic method needs to be tested against the best current, saying "well what does that mean? Is it the best in the whole world? Or is it the best current in the situation (which may be nothing)?" And would you have any views on ... not only the ethical underlying principles but what that text implies.

EC16: Yes well again, I mean I'd agree with what you said. The best current suggest or implies available. The currently available is what they presumably mean.

RC: Right, so that's how ... that's the initial implication. It would be harder to read into that "the best existing"?

EC16: Well the best existing would ... you see the best existing would be ... could be unhelpful because you may be using ... you may be using the 2nd best line of defence on something because you can't afford the best...

RC: Right.

EC16: So – best available. Yeah I would have thought so. But in fact I don't know even if one even needs to say best. Should be tested against "currently available" – why say "best"?

This represents another challenge to the use of the term "best" in this context.

Further, another passage of interpretive comment illustrates that, in the final analysis the issue of the standard of control arm and the issue of placebo controls effectively do merge at many points. The interaction is instructive:

RC: Well, thank you, I just wanted to clarify one other thing to make sure that I understand your use of the terms. You mentioned equivalence and non-inferiority ... uh superiority trials and equivalence trials. Could you just, in a nutshell, mention, so that I'm clear what you mean by those types of trials?

EC7: I tend to use equivalence and non-inferiority studies as being much the same.

RC: Synonymous?

EC7: While the superiority trial is where you are trying to show that the new drug is better than either placebo or an existing drug.

RC: And the non-inferiority would be the new drug up against a placebo?

EC7: Well not ...

RC: Or the equivalence...

EC7: Well the problem is... one can either look for equivalence, that they are exactly the same, or that some people define non-inferiority, I believe, as that the new drug is at least 90 percent as effective as the existing drug.

RC: I guess where I'm not clear is – could you not do those types of study head-to-head with your competitor's product as opposed to against placebo? What I'm not following is why that's an argument for placebo in the eyes of ...

EC7: Well, they're saying: (a) you don't know what the effect ... the real effect of the comparator in your study is. You are assuming that it's going to be the same as in previous trials.

RC: Okay.

EC7: And you're not allowed to assume that ...

RC: Oh, I better clarify my question – you said that increasingly people are moving towards doing non-inferiority studies rather than superiority studies...

EC7: I mean one of the reasons for that is because there aren't new types of drugs coming through, so many of these are "me too" drugs where people have just slightly modified the molecule and it's really the same sort of drug that's being tested so from the start they're not expecting it to be better than what's already on the market. Whereas with superiority trials you hope that what you have is going to be better either than a placebo or better than whatever is already the market leader.

RC: What I wasn't quite clear on was ... you used that example in the context of why there was support for a version of the Declaration of Helsinki that eased up on restriction on placebo. I guess I'm not entirely clear why the move to non-inferiority or equivalence studies is also wrapped up with a desire to liberalise the use of placebo? Could you not still do those studies head-to-head with the actual other treatment?

EC7: You could do head-to-head but it becomes more expensive and it takes longer.

RC: But how is it ... a non-equiv... sorry an equivalence study would generally study the effect of the new drug against a placebo – is that what you were saying?

EC7: No no. An equivalence study is going to study the effect of a new drug against an existing licensed drug.

RC: As a superiority study would as well – would it not?

EC7: If you thought there was going to be a superiority. But so often nowadays there are "me too" drugs and so it is presented as an equivalence study. There's no expectation that it's going to be any better than what's already on the market. But if you can get it licensed, if you can show that it's as good as what's there already, then you can get a license for it and try and by your marketing skills carve out a little niche in the market for yourself.

RC: That's what I thought was the case. That's what I thought you meant by those studies. Where I guess I seek more clarification is how does that relate to the argument about the placebo restrictions in the Declaration of Helsinki or does it?

EC7: It relates in that because of the difficulty of doing equivalence studies, what the manufacturers would prefer to do is a study against placebo because the difference would be greater, the number of patients you need short ... smaller, the study would be over quicker so you've got more patent ... protected patent time available. If you get the licence, so you know financially your pharmaceutical company is a great deal better off but in the process you have done a placebo study when there is already a known beneficial drug that you could use in that situation and so you have put patients potentially at risk by not allowing them to have it and let me give an example. A couple of years ago the [ethics committee] that I sit on was sent ... a study for approval of new glitazine type drug in type II diabetes. The inclusion criterion was that treatment of type II diabetes by exercise and diet and non-pharmaceutical methods had failed and that therefore the person needed drug treatment. The proposal was a 9-month trial of this new glitazine drug against placebo and our feeling on our committee was that if you've decided somebody needs pharmaceutical treatment, to leave them without it for 9 months is to run the risk of complications of diabetes developing, and so we rejected that study and said this is not possible. You've got to use an active comparator. ... And the problem is, we then said ... we're told 'well okay, we won't do the study in the [EC7's country] but we're being allowed to do it in [name of 2 other developed countries], so we'll get on with it there'.

This extensive discussion helps to bring together the discussion of the interpretation of Paragraph 29 (+ NoC29) both in respect of placebo-controls and the standard of

comparator arm. It raises another thorny issue in all research ethics. Is it ever justified to approve research that is, arguably, on the margin of ethical acceptability (or perhaps even acknowledged to be across the boundary into "unethical" territory) on the grounds that the supervision of research in the particular jurisdiction being asked to approve the research is thought to offer greater overall protection for research subjects than if the project was turned down with the result that the research is then conducted off-shore.

Another of the commentators (EC4) saw the shift from "best proven" to "best current" as decisive in the interpretation. This commentator saw the term "best proven" as a requirement that the control arm be the best proven "anywhere in the world". By a change to "best current", it now means "current in that country". The commentator went on to state:

EC4: ... So I didn't really understand why this fuss was made because the best current seems to be when you look at it from a cultural point-of-view, acceptable. From a strictly high-handed ethical view, this is ... the um ... the former trial would be better. That's why maybe it didn't give rise to any criticism whereas the current can be relative to the country and it can be nothing or very ... nothing or whatever, I don't know, but this is imaginable.

Further discussion will be postponed to the overall summary of Paragraph 29.

6.3.2.3 The Status of the Note of Clarification

No clear cut statement about the relative weight to be given to the text of the paragraph itself in contrast with the "Note of Clarification" (NoC29) has been promulgated by the World Medical Association. A prima facie argument could coherently be advanced that a "Note of Clarification" must inherently be less "authoritative" than the text itself. However this is not a straightforward issue and gave rise to a few observations among all three groups, for example in a discussion about whether the appending of NoC29 constituted a "6th" revision:

RC: ... they formally added it in the Declaration of Helsinki in 2002 but they didn't refer to it as the 6th amendment ...

MR12: Oh no no ... yes, I accept that. But then technically it isn't an amended article.

It should be noted that for the purposes of this thesis, NoC29 and NoC30 have not been treated as revisions (the preamble to the DoH seems to allow this as it refers only to "Note of Clarification ... added" rather than as revision [WMA, 2004]) and throughout has referred to the 5th (Edinburgh, 2000) revision as including these Notes.

6.3.2.4 Summary

Before finishing the discussion of Paragraph 29, reference should be made to an insightful observation about the entire authorship process of the DoH by one of the medical researchers interviewed:

MR12: there's always been a problem writing a policy document by committee. Because at the end of the exercise if it's truly been done by a group of people who aren't absolutely unanimous then there are always some tensions and you end up

with verbiage which seems to satisfy the most common ground that you can identify but no-one's totally happy with it. And ... we have to recognise that that's almost inevitably the case with the Declaration of Helsinki as with lots of other documents.

In the context of Paragraph 29, this should be put alongside the same interviewee's remarks:

MR12: You can dissect these statements ... if you really put them under a magnifying glass and dissect it phrase by phrase, word by word, there are actually lots of bits all of us in some way would have a personal view as to how it could be more clearly expressed.

With respect to agreement in interpretations of what the "landscape of medical research ethics" looks like, arguably this paragraph demonstrates the greatest disagreement of all. To push the metaphor further, one can almost imagine two groups standing implacably back-to-back facing completely different landscapes! When it is considered that the placebo controversy arose in a context of studies in developing countries (in settings where placebos would never be permitted in the developed world) but quickly moved on to the use of placebo in any context because of regulatory requirements this is perhaps not surprising. These are two overlapping but very different situations yet the same instrument – Paragraph 29 + NoC29 – is being used to address both.

6.3.3 Paragraph 30: Post-research duty of care

The interpretation of interview responses regarding this highly controversial inclusion in the DoH was complicated by the concurrent debate over the content of the Note of Clarification (this will be referred to as NoC30). Following the formal

adoption of the Note of Clarification to Paragraph 29 (NoC29) in October 2002, a working group was established to consider whether to modify Paragraph 30, add a NoC30 and, if so, what would be the text of the modification or NoC30. Since all of the interviews took place before the text of NoC30 that was eventually adopted had been agreed, the task of analysis of the interview data for this paragraph differs from all of the others in that it took place in the context of actively searching for an actual text for NoC30.

Notwithstanding the debate about NoC30, there were a number of interpretive phenomena observed with respect to the original text. Not surprisingly there was comment on how to understand the term "best proven". However, the key interpretive feature for this paragraph was the nature of the obligation created by the phrase "assured of access".

A further interpretive debate regarding the requirements imposed by Paragraph 30 surrounded the fact that the paragraph seemed to imply that – contrary to usual scientific practice – the results of the one study should form the basis for ongoing treatment decisions. What if the results of the one study seemed to be at odds with other similar trials?

Authors

An important interpretive point relating to an ongoing post-research duty of care was that, if it was seen that the sponsors had such a duty, how long did that duty persist? This was a matter of significant disagreement in interpretation.

One author's views, illustrative also of the aspirational intentions of the document could, arguably, be described as a "middle ground" approach:

A7: ...we had heated discussions about that, realising that depending on how you answered that you might shut down research frankly. No, probably something short of life. Something more than a week. So now we can narrow the distance. Again, I think what it comes down to is, if in fact, researchers, the research community begins to buy the necessity of valuing the population that becomes the study subjects, then in fact what's acceptable today maybe ... again like best practice ... may become a moving target. You know an acceptable public education 150 years ago was you could do a little reading, you could cipher a few sums and you could sign your name. Now we would frankly call that functionally illiterate today. ... So is this a foot in the door, is it a start, yes, probably. And what we define as ideal is probably far more than what would functionally occur. But I think it is strong statement that says "Helsinki was intended to protect populations and not just populations of people who look and act like you do".

There were, however, others who saw the possibility of a life-long duty-of-care as what was envisaged:

A14: Some of the thinking came out of some of the AIDS trials in Africa. That from a moral perspective that we had an obligation, if we are going in and particularly providing treatment to people who did not have treatment before, that there was an obligation to continue.

RC: Now one of the ... and that potentially could be for the rest of that patient's life?

A14: Yes.

The difficulty of accepting the results of a single study and applying them to the ongoing post-research care of the patients gave rise to some divergent views among

the authors. The wording of the paragraph is "assured of access to the best … methods identified **by the study**" (emphasis mine). One author, after initially suggesting that the paragraph did not explicitly require the results of the specific study be applied changed view when the specific text was again pointed out. This author went on to make a point that did not arise in any of the other discussions of this matter – that the post-trial duty of care involved a requirement to conduct further research in that specific group of people:

A7: So now you've in fact laid out the next study. Is there something different about this population?

However, other authors considered this apparent implication of Paragraph 30 to be another case of taking one paragraph out of context and drew on the impact of Paragraph 29 and the term "best proven", stating:

A14: It has to be taken … you can't be reading things in isolation. It has to be taken in the context of what came before… number 30 is an example … or number 29, sorry, is an example. So no piece can be taken in total isolation. It [Paragraph 29] does not mean that the "best proven" happens to be what came out of the result of that trial.

However, for the most part, the debate seemed to assume that there was a generalisability of the results of the particular study and those of other similar studies, at least for the purposes of the interpretation of Paragraph 30. One author in particular cautioned:

A9: So in all cases we would caution that this paragraph not be taken out of context and only read by itself but that it's read within the context of the whole of the

Declaration of Helsinki which, really, if you look at Paragraph 2 it says it's the duty of the physician to safeguard the health of the people.

One of the authors expressed the following as the way of interpreting this paragraph and getting around the apparent difficulty of the application of results of a single study. This dialogue occurred in the context of a question about a study of (hypothetical) "drug A", which shows benefit, but simultaneously another study is published showing "drug B" to be superior to "drug A". How would the requirements of Paragraph 30 be interpreted?

RC: That doesn't commit you to keep going on A?

A3: No! It commits you to one thing, if the patient has benefitted the benefits must continue. It doesn't say you can't give them better benefits. What it says is you can't say "I'm finished with you. Go back to no treatment".

RC: And if no-one else can pay, is it the sponsor's responsibility?

A3: If no-one else can pay, you should have considered [Paragraph] 19.

A key concern with respect to ongoing duty-of-care – if that duty was placed on the sponsors of research - was that it may unintentionally impair research proposed by academic institutions. Multinational pharmaceutical companies would have the benefit of an income stream from the successful trial of a product in development. Universities would not.

A8: Multinational corporations - their budget is sometimes more than a budget in an average country in [the developing world] or anything like this - we are dealing also with ... research in a university hospital or any other institution which I think ...

puts a burden which would be impossible. So maybe that is something that needs to be clarified. … You know this is one thing that we have to think on.

Medical Researchers

In an almost exasperated tone, one of the medical researchers expressed the apparent difficulties with the requirements of Paragraph 30:

MR17: Yeah, of course, it's in our hands so if we uh ... ask the investigators to go on with the drug in those patients and we will provide the drug it's no problem. The other thing is that, some investigators won't like to do that and maybe that's not really clear here in the Declaration what the obligation of the investigator is. Because the company has to provide the drug ... ongoing ... to, or to the patients who participated in a clinical trial. But what is the obligation of the investigator because some investigators tell us: "Well for the one or two patients who really like the drug ... I'm not going to uh ... put energy in a follow-up trial. So they refuse to give the experimental drug to the patients after the trial is completed. So even if we would like to do that the investigator blocks it. So, that happened once. And the other thing is, what I already told you, that when the compound is registered and we stop the uh ... the uh ... follow-up programme because the drug should be available on the market and when it is not fully reimbursed and that differs from country-to-country, when the patient has to pay for it, do we define it as fully accessible for a patient?

This very clearly illustrates a number of interpretive points:

1. Different companies can clearly decide for themselves what their obligations are to the study participants
2. What to do with patients who seem to benefit from the drug that was not shown to be superior overall in the study – the strict wording of Paragraph 30 would suggest that the better of the study compounds should be made available and it apparently leaves no scope for provision of other compounds

where individual patients, in an idiosyncratic response, seem to benefit more from the "inferior" drugs in the study

3. What is the interpretation of the phrase "assured of access" – is access assured once a drug is licensed (subject to ability of someone to pay) or does assurance of access require funding as well?

The same insightful views of the same medical researcher asked the following questions:

MR17: So, if we do a phase II trial, let's say it's a placebo controlled trial, we do a phase II trial with let's say fifty patients, and we see a trend that this compound is better than placebo, is that proven? Probably not. So I think we have a point there that we don't have to install a compassionate use programme, but when you do a phase III trial with a thousand patients and you have the results of one, this one trial and your compound is better than placebo or the comparator – is that proven? When you go to a regulatory authority they probably say no, we need two trials to have proof. So I think the word proven here is very important. So I ... I ... I think you can raise the question, based on article 30, can you install a compassionate programme at all because probably the authorities will say it's proven when we decide that you can register the drug and even then you can even raise questions because they always ask additional ... um ... safety data after the registration.

This again, returns to the central question: what does "proven" mean?

As an interesting and important aside in the context of statistical testing, it may be seen as more difficult to prove that a particular new drug is no better than existing compounds than to prove that it is better. In theory, according to traditional statistical hypothesis testing, a single result that gives a p-value under a certain level could be considered sufficient evidence of a difference. So if, for example a study achieves a

p-value of less than 0.01 then it may seem reasonable to consider it "proven" that the new drug is better than the old.

However, proving no difference may be more problematic. This depends on the power of the study – a value that depends heavily on the sample size. So if no significant difference is found and the study has a power of 0.8 (generally considered sufficiently powerful) then does this "prove" no difference? Why should a different probability be accepted for "significant difference" than for power to show no difference?

However, to achieve a power of 0.99 (the inverse of a significance level of 0.01) would require a manifold increase in sample size. So, in many respects, proving no difference is several-fold more difficult that proving a difference. Even so, as the interviewee points out, the results of a single trial are seldom accepted as conclusive.

Another tricky point emerging from various attempts to "interpret" Paragraph 30 relates to the fact that, if the obligation for post-research provision of the "best proven" treatment shown by the study falls upon the sponsor, what happens if the study actually shows it is not the drug manufactured by the sponsor that is shown to be "best" in the trial. This is well-illustrated by the following exchange:

MR20: So the assumption is that 'best proven' might not be the newest one?

RC: Well this ... that's right.

MR20: The prior probability of the new treatment being better than the existing treatment on the basis of the evidence that I've seen is about ... equal. It's 50/50.

RC: That's been one of the objections raised to this paragraph.

MR20: It actually doesn't say that it should be the new one, it just says the best.

RC: That's right.

MR20: And that's very interesting because there are actually quite a lot of examples one could give of the standard treatment actually turning out to be better than the new treatment.

RC: That has been one of the objections raised to this as it would seem that – what if drug company B is trying to develop this new treatment and it turns out that drug company A's old treatment is actually better, this seems to put a requirement on company B to provide their competitor's product for the trial participants which they have no control over the production of and ... if company A stops producing it ...

MR20: I must say that given that there are so many gross distortions in the research agenda and indeed the health service purchasing agenda, I must say that I haven't actually given great thought to this particular issue.

Another of the medical researchers made the following comments regarding post-trial duty of care.

MR18: ... medicines don't exist in a vacuum, they exist within a care environment and very often the provision of a care environment in a clinical trial is possible but that care environment um ... outside the clinical trial is very difficult. Um ... let me give you an example of that we ... we've been doing a big programme on obesity. And which is still ongoing. And ... but that ... obesity's not just a drug programme ... it's um ... it also and indeed nobody would want to treat obesity with just drugs. Obesity's all about um ... sort of health care programmes, dietary programmes, nutritional programmes, etc., etc. And drugs are just a component of those programmes. If, at the end of the trial, we wish to meet clause 30, we would presumably have to maintain not only the drug programme but health care programmes in the environment which is extremely difficult for a company to do. To set something up and run it for 6 months for a trial is one thing. To run it for 10, 15, 20 years – there's no time limit there – how do you actually do that? So, um ... the concept is good in the sense that its an anti-abuse concept. It says don't use people

as guinea pigs for a clinical trial and then drop them. But the practicality of meeting the concept is actually very hard. The way that that for a number of people have interpreted that is don't go places where the provision of medication would fall back on the sponsor after the trial. And that, in turn, moves research away from the poorer countries back into the richer countries on the basis that the individual, the health insurance, whether state or private, can provide and so you end up in the environment where clinical research becomes more and more something um ... in the rich countries for the rich populations. So ... and this is part of the general concern that if you in the attempt to ensure that you don't put so many barriers in the way that poorer people are ignored. And I think that's the danger that comes out of something like Clause 30. But I think the aims of Clause 30 are fine. I think the practicality is very difficult and the response so far has been very muted. I don't think there's been an awful lot of discussion about it except to say that its very difficult.

Does this represent a situation where a single paragraph of the DoH is being interpreted on its own and out of context? Or, on the other hand, is this a valid concern about the requirements of Paragraph 30?

A further question that seems to emerge in considering this interpretation: does this demonstrate relative difficulty on the part of those involved as stakeholders in medical research to accept the DoH as an aspirational document? Clearly the "ideal" with respect to the treatment of obesity (the specific condition provided as an example) would be an ongoing holistic treatment programme. However, even resource-rich parts of the world struggle to provide such for their populations.

Another of the medical researchers pointed out that Paragraph 30 (and broadened and comments to the DoH more generally) either had to remain as a general set of principles or to have very extensive clarifications. This researcher (MR8) felt that the CIOMS document should fill that role (although conceding that CIOMS was written

by a different organisation) and that the DoH should refer readers to the CIOMS document or that the DoH would have to be re-cast as a document closer to the CIOMS guideline in length.

Some comments by the latter two groups, "medical researchers" and "expert commentators" do not specifically address how they would interpret the wording but how they have observed ethics committees or others interpreting the document. This can often be instructive with respect to interpretation issues pertaining to the text and so, where insight on interpretation is offered, these views are included in this analysis. One such comment was:

MR12: .... we know that there are some ethics committees, and we know from the debate in Helsinki that there are individuals certainly who see ... who feel that article 30 creates an opportunity to insist on continuity of medication at the end of a study. And we're not saying that in all instances that that's not a legitimate stance to take because we currently would do it in the most obvious instances but it's the fact that there's a looseness about the wording of 30 which if folks who feel they may be able to control how many protocols are implemented and particularly what should then happen after individuals cease to be actively participating in the study, it does open the door to them to try to derive more from Paragraph 30 than we would feel is always justified.

This particular comment occurred in the context of a justification as to why previous versions of the DoH (in particular either the 1989 or 1996 revisions) were often quoted and the 2000 revision not.

Another medical researcher very succinctly summed up the difficulty with interpretation of Paragraph 30:

RC: The other part of Paragraph 30 that people have found some interpretation difficulties with is that phrase "best proven"?

MR2: Well exactly.

RC: Any comments on that?

MR2: Therein lies the dilemma!

Finally, in many of the interpretive efforts, unique views were expressed that were not noticed, or at least not mentioned by any other interviewer. The following is an example taken from interview dialogue in the context of Paragraph 6. However, its consequences lie in interpretation of Paragraph 30:

MR6: If you say this is new, then this is contradictory to what 30 wants to do.

RC: How so?

MR6: How? Well because 30 has made it concrete that you must make available at the conclusion of the study ... and here it says continuing studies are still needed.

RC: Yes. Does it have to be either/or or could it be both/and?

MR6: It could be a contradiction. They could both apply. As far as reasons ... we have dozens of antihistamines; none of them work well, but they all work a little bit. So they continue to look for one that's better so you wouldn't throw out those that are moderately good because they weren't perfect. And don't let the perfect be the enemy of the good ...

Is this hair-splitting or is this an insightful and decisive observation exposing a deep and important contradiction at the heart of the DoH? On the one hand the document specifies what should take place "at the conclusion of the study". On the other hand, the document prescribes that research should be "continuous" meaning, at least on one interpretation of "continuous", that there is no such thing as "time after the

study", provided "the study" can be interpreted to be all such studies. The Declaration is suggesting that a state of "study" is a never-ending situation. Certainly there is an element of truth here as typically even after phase III trials have ended, when a drug has been licensed and is now being prescribed, there is very often a period of more intense monitoring. It would probably need to be concluded that trying to see this as a loophole to avoid ongoing provision would be a rather disingenuous interpretation as it would be very difficult (perhaps even impossible given the results under the "Authors" section above) for this to ever be seen as the intent of the WMA. .Certainly in the case of a "living text" (defined for the purposes of this study as one capable of being modified, as the DoH is) then the authors can respond to significant misinterpretation with a change of wording or addition of further explanation. Indeed this is what was taking place concurrently with these interviews; the WMA was debating an amendment or note of clarification. However, it was never with this perceived contradiction in view.

Another of the medical researchers expressed a number of interpretive difficulties that are summed up in the statement:

MR3: My trouble with 30 is that ... first of all you can't figure out what it means and 2nd of all it's not nuanced and it doesn't give adequate guidance.

These interpretive difficulties encompassed the following the extent of the obligation:

MR3: Does it really mean that having treated one migraine you now owe them migraine therapy for the rest of their lives? ...You do a 4-week or 8-week hypertension study and you show that the drug lowers blood pressure. Does that mean you're responsible for their hypertension? For one thing, you have to set up a unit to monitor blood pressure ...

Having expressed these concerns, however, this researcher acknowledged a post-research duty-of-care in some situations:

MR3: With a cancer trial where you really wouldn't want to stop effective therapy, you never do stop effective therapy, you only stop ineffective therapy. So it doesn't come up there. You could have a discussion about AIDS ... you know it's a really bad disease where stopping the therapy's going to make them sick. You better make some arrangement for knowing what you're going to do with these people. Whether it's your job to complete it or it's the local country's job to complete it we're not ready to say, but you should think about this and it should be part of your plans. But like all of these short sentences it's not nuanced.

These examples will be considered again in the discussion of how the three groups tend to use specific examples. The key objection in the interpretation of Paragraph 30 expressed herein is what appears to be a "blunderbuss" requirement – rather than a well-targeted statement. How a well-targeted statement (a "nuanced" statement) might be worded was not, however, discussed. Although this researcher expressed support for the proposed NoC30 – a statement that, however, was not eventually adopted.

There were further difficulties around the interpretation of Paragraph 30:

RC: You were talking about not accepting the results of one study ...

MR3: You could argue that until somebody's looked at this data you don't really know what the results are. So whether it's really an obligation ... the other thing that

is that what we are nervous when people maintain a drug very long when there's no experience with the drug. Maybe this is the 1st trial and nobody's ever had it for more than 30 days. Are we really ready to put people on it for 6 months? I mean you might but you want to think about it.

When questioned further, the interpretive focus turned to the meaning of the word "access":

RC: Some have said that a lot hinges around the words 'assured of access' and have said that that stops short of assured of funding but simply means assured of access. The funding may have to come from somewhere else.

MR3: But even access. This drug may not be ready for long-term use yet. Also you don't know if it's ... I mean it uses the term 'best therapy shown by the ...' I don't know what that means. It means an effective therapy ... more effective than placebo, better than anything else in the world. I mean 'better than anything else' is an extremely unusual outcome of a trial. The 1st proposed fix for this was Paragraph 30. I basically said 'well sure you may have to – yes, if it's the best therapy anywhere, if it's been replicated so that we know this from several places, and if the regulatory authorities have approved it, then you owe them'. I mean how many times does that happen. And how long after they were in the trial does it take? It kind of renders the whole thing meaningless.

Expert Commentators

One interviewee spoke articulately about the controversial nature of Paragraph 30, illustrating with examples why the controversy applies to both developed and developing countries, before acknowledging, however, that unavailability of post-trial care may be more pressing an ethical difficulty in serious diseases in the developing world. In this regard, we can see that some expert commentators are "hedging their bets" with regard to a clear opinion regarding the so-called "double standard" of research ethics between the developed and developing world.

EC5: Now ... um ... obviously this is controversial for preci.... And it wears its controversy on its sleeve. It's about making sure that people who have a chronic illness, or at least uh ... an illness which takes a very long time to treat, or whose natural history may or may not be self-limiting um... shouldn't be put into a trial of say 3 to 6 months and then as soon as that ... as soon as their 6 month time in the trial is over, pulled out, pulled off whatever medication they're getting, or whatever treatment they're getting and re-assigned back to standard. And it's controversial as much in the [interviewee's home country – a developed country] as it is in South Africa or Brazil because if you think about multiple sclerosis or Alzheimer's dementia or rheumatoid arthritis or uh ... cancers of various kinds then most of these people will need to be on medication for years. Uh ... in all because you're trying to slow the progression of the disease, or prevent remis... not prevent remission prevent relapse or whatever it may be. Uh ... schizophrenia is a very good example because there have been lots of antipsychotic trials in recent years where the licensing trial required patients to be on a drug for 6 months and then they'd be ... then the trial would close and often times, the controversy would be between the sponsor and the [funders of health care in interviewee's home country] context about whether the trial had proven that the drug was effective. And they said that if they had proven that it was effective, or at any rate they'd licensed it, that the responsibility was on the [funders of the health service] to pay for it now. Whereas the [funders of the health service] in many cases was saying, 'well it's quite unethical to start someone off on a drug and then provide it to them afterwards and did you tell the person they might not get the drug afterwards? No, you didn't so the responsibility is on you to keep providing it'. So they're fighting over where the financial buck stops. Um ... now, this gets, of course, much more acutely concerning when you're in a situation where the health care resources are very uh... sparse uh ... for instance, if you happen to be HIV positive in sub-Saharan Africa then it matters a great deal whether you get some antiretroviral um ... in an effective dosage regimen antiviral, and if you're started on it, and given it for 2 years and then given nothing afterwards then you can have a nice debate um ... and I heard a paper by [one of the other Expert Commentators] arguing about this, about whether it's better to have 2 years of life on antiretrovirals and extend your life for 2 years than not getting anything at all. Or whether you should uh ... get antiretrovirals for the rest of your life simply because happen to have had the good fortune to have been enrolled into a clinical trial. So the interpretation of this uh ... is open and the response of the pharmaceutical industry is uh .. hasn't shaken down to a settled position on this yet. A lot depends on how uh ... forceful a research ethics committee is in in asserting that this principle means that patients at the end of the trial should get whatever is ... turns out to be the best treatment from that point onwards and they shouldn't be denied it on financial grounds alone.

The difficulty with any sweeping requirement such as this, and the need for robust local review mechanisms, was strongly advocated by another of the expert commentators:

EC11: I was saying earlier that I wouldn't want to make completely sweeping judgments about these things. I mean that's a perfect example of why ... you would absolutely want that kind of initiative to occur. On the one hand, you know getting back to some of the other wording in the modification, on the one hand we're not talking about high risk here, we're not talking about a population that's going to die without this innovation etc. etc. We are talking about something that would be useful for the local population. The issue becomes, then, not whether or not it should be done in principle but how are we going to evaluate ethically if it's going to be approved locally. Again you constantly get back to ... I think if one tries to pretend that one can absolutely draw lines outside the context of knowing for sure that they're going to be exactly the kind of counter-examples you just came up with, the debate will never end because it will just remain polarised. I think one has to look for a balance and the balance is a procedural balance. I mean the balance procedurally is ... some of these questions clearly are not going to be answerable to either one polarised side of the debate or the other. What is the case is that we should proceed unless we know that since it's going to be the most rational, and effective, and coherent and consistent compromise imaginable. Now to do that we've got to ensure that we have a review process in that local population that optimally works. The problem is that in most of these populations we don't at the moment.

Another of the commentators, when asked specifically about whether "access" might mean "availability through licensure" rather than "funding" for the treatment, responded with some surprise that some had expressed that view. However, in the view of this commentator, access implied funding as well as licensure:

EC17: Right, I hadn't seen that loophole actually. But I suppose yes they could argue that you've got access to it, all you've got to do is pay for it. Well I think that what I said earlier would apply that I think it would be very sensible for the host countries to, since that's got to be required ... that the people should have these treatments to insist that the sponsor pays for those treatments or other methods. Otherwise I mean it doesn't say very much at all, does it? Have access to it well

that's I mean I suppose everyone in the world's got access to any existing treatment – all they've got to do is pay for it.

Another of the commentators expressed disdain for the wording of Paragraph 30 in no uncertain terms, interpreting its requirements as "impossible":

EC20: Well here ... this is a horrible paragraph. It's awful. It's awful both from the way it's written; it's awful from what it's trying to do because it's just impossible. At the conclusion of the study you know who's going to conclude a study who knows what a study is. A researcher may have end points that they're testing for ... does that mark the end of the conclusion of the study? Is a study concluded by the premature ending, the termination of it by a sponsor? Does it depend what kind of reason for termination? Suppose they decide they haven't got enough enrolments so it's concluded. Suppose they say 'no, it's too expensive'. Suppose they say, 'we're not getting significant enough results'. Very different kinds of reasoning. Also the questions about what counts as one study. This is 'the' study and it's ... it looks as though it's got temporal boundaries around it rather than thematic boundaries so for example you could say that a phase I, II, III counts as one study. What about phase IV? Is that still under the study? Reporting conditions, monitoring conditions are different. I personally can't say what counts as a study and to that extent I wouldn't be able to give anybody guidance as to what this meant and to how to interpret it, all I can say is what I think it is. Again, that's the question of distinction between concluding the study locally and a multicentre study, multicentred conclusion – so, problems there.

Interpretation of what is required after the research is finished, in a similar way to the interpretation of "best current" in Paragraph 29 (see above), is seen by this commentator to hinge around interpretation of the term "best proven":

EC21: The other issue I think is the meaning of the word "proven". You can use that word in such a way as to effectively say "nothing's proven". You could also use it, I think rather dangerously, by saying "well one trial has shown this". So I think we need some clarification and each institution has to work out its own sense when something's proven, when it isn't. We need some clarification of what the boundaries of that word are designed to entail. I mean lawyers use the word "proof" in one way.

My impression is very strongly that the scientific community uses it in a rather different way. More and more these documents are coming to be interpreted by lawyers rather than by scientists. Ideally by someone who is both but that doesn't happen often.

Issues of discipline-specific epistemology (knowledge-claims) lie at the core of the debate about the meaning of "proven". This interaction with one of the expert commentators illustrates this well:

RC: When a lawyer looks at a medical ethics situation, as you say documents like this are increasingly being looked at by lawyers, which standard do they use?

EC21: It's a damn good question and I don't think there's an easy answer. My own observation is that lawyers whose primary responsibilities is to keep institutions out of harm's way tend to adopt very stringent standards. In other words, they'll say "You shouldn't do this unless it's very clear indeed that something is effective". ...I tend to come at it from a slightly different perspective. Sadly influenced by the fact that one of my other interests is criminal law so I tend to look for a fairly high standard. A colleague of mine [...] is both a lawyer and a philosopher. [...] tends to come at it from the perspective of a lawyer filtered through philosophical analysis which to most lawyers is, I wouldn't say it's anathema, because we don't understand it not ...

RC: So it's logic ...

EC21: Yeah.

RC: Formal logic. ...

EC21: And the lawyer was coming at it from I think almost the perspective of the person-in-the-street, the juror, "How are they going to weigh these things? We can articulate the test however we like but what's common sense going to tell us?" And I think you do end up with a certain amount of diversity of opinion around that word and it would be useful. I wouldn't personally want to say "the best scientifically proven" because I think that would cause some real problems but is it possible to insert some clarifying note which gives us some clues for standardisation purposes as to how one might interpret that word "proven"? ... And indeed, that goes to the question of "should be assured" by whom? Perhaps that's really in a long-winded way what I've been talking about. Whose responsibility is it to assure access? If you

say the government of [country] ... well they assure access by saying "well we approve the drug". [Another jurisdiction] may well say "well we assure access by putting it on the pharmacopeia so it can be paid for, for example, by [insurance company]" ... What about the drug company? Is there an obligation on the drug company to ensure that there is a sufficient supply?

As mentioned above, one of the expert commentators was concerned about the use of the word "best" both in Paragraph 29 ("best current") and in this paragraph ("best proven"):

EC8: Right, there is a point at which responsibility ends and should end. Now if in fact, if in fact, it's only a drug company that has the responsibility or the researchers in the drug company then clearly the farther you move the less feasible any of this becomes. But if, in fact, the original negotiation involved the Ministry of Health and perhaps an international agency of some sort then ... such as the Global Fund you know, or some other kind of activity – either the obligation ceases after a point and that's what's written into the original negotiation or if people still need a life-prolonging drug, maybe they'd only get "the best" if drug B has continued to be effective. It doesn't follow that they have to get the best and that's why "established effective" is better wording that "best".

Another of the expert commentators saw an injustice in providing ongoing treatment only to those involved in the research, the reference to "goody" meaning someone who had taken part in the research study:

EC19: But aren't you saying there – almost amplifying what I'm saying – that if you can't afford everybody to have this, you're saying that "you can because you're a goody"?

Another of the expert commentators also spoke about the interpretation of "best proven" and made the additional point that application of this paragraph may

actually remove properly constituted decision-making power from appropriately appointed administrators whose authority is legitimate:

EC3: I think secondly it may be ... who is to say what is the best proven method? I think I can see ... I can interpret very many different intents here but I think the stark statement without qualification will do nothing but create problems. So, for example, ...in [name of country], drugs are approved by the ... government, ... but whether or not they'll be paid for is a different level of decision that will be taken by insurance companies and by [local] funders. ... I'm not sure ... I can't interpret this paragraph in a meaningful way. I have, in my previous career, been senior administrator of the [name of hospital], responsible for resource allocation decisions and while I thought I behaved compassionately in a senior role, this would take decision power away from me that I would not allow had I still been in an administrative position.

A further view of one of the expert commentators, basing interpretation on their own experience:

EC3: ... 15 years I have had membership of two [ethics committees in commentator's own country]. This now is one of the protocols and, of course some things sit morally absolutely correct. If this thing proves to be good, why should the people ... you rewarded them in some sense. This might be ethically naïve because you could argue, well, there are trials where that anyhow the duration is limited or it's a life-and-death issue or it's advanced cancer and then ... so why should one make a rule? Is that somehow unfair? One should ... yes, there should be a ... a note of clarification explaining when this is important and maybe more in chronic disease than in acute disease ...

6.3.3.1 Summary

Surprisingly perhaps, given the sudden nature with which Paragraph 30 was "sprung" on the research community (see Chapter 4) there is a surprising degree in which Paragraph 30 achieves agreement in the description of the "landscape of research ethics" across the 3 groups in a way that could be described as follows. There seems almost universal agreement that the division between a research

participant's longitudinal life experience and the horizontal nature of the conduct of research gives rise to important ethical considerations. Research projects, by nature, must have a beginning and an ending after which publication ensues (perhaps multiple endings in this regard but these are all horizontal events). Most research projects come to an end and the research participants continue living their lives. That there is an obligation to consider this fact and the duties it gives rise to has almost universal backing among interviewees. The outstanding questions surround the particularities, summed up by one "expert commentator" as "Who owes what to whom and why?" The discussion in the 3 sections above illustrate some of the details, some of the parts of the "landscape" that are still described very differently..

6.3.4 Paragraph 19

There were three main points of interpretation with respect to Paragraph 19 that deals with the reasonable likelihood of benefit to the population from which the research subjects were drawn. They are interpretation of the phrase "reasonable likelihood", definition of the term "population" and the question of whether the strictly logical application of this paragraph might be seen to call into question whether research on healthy volunteers is ethical to conduct. The first two will be dealt with together as they occur in the same phrase and interpretive points often intermingle.

6.3.4.1 Paragraph 19: "Reasonable Likelihood" and "Population"

The definition of the term population occupied a great deal of the thought that went into interpretation of this paragraph.

Authors

There was a broad interpretive approach to the definition of the word population, illustrated well by one author's comment:

A15: ... my interpretation was that the word "population" was context-specific. So it does not mean necessarily the whole population of a country – it could mean "gay men of Jewish extraction" ... and in my view it never meant the entire population of the country, state, region or administrative district

Another author adds another dimension to the definition of population and spans the two major interpretive considerations in relation to Paragraph 19. With consideration of the concept of time, an important linkage is formed between the population of "healthy volunteers" and the requirement for a "reasonable likelihood of benefit" to the study population:

A7: Well, unfortunately, our status today changes on a regular basis and today's healthy volunteer is tomorrow's recipient of health care.

RC: So the concept of population has that time ...

A7: Absolutely ... absolutely.

RC: Right, I guess that's what I was starting to explore is what you had in mind when you said population. Is it population of a country or is it a much more flexible concept than that?

A7: I think it is fairly flexible but I think the specific discussions had to do with the fact that again you don't subject people to risk from which there is never any intention they would benefit okay. But we all know, of course, that we must have

healthy volunteers for some of our research otherwise we simply couldn't advance the healthcare process.

In the context of the possibility of a Note of Clarification to Paragraph 19 (and the ongoing discussions about NoC30), this same author made the following insightful remark:

A7: To the degree that the language substantially, repeatedly in large groups, raises the concern, I think you must look at the language. To the degree that there are small, very outspoken groups who say "I read it different than you do", I would prefer not to see clarification because in fact if you get a thousand readers you can probably find a thousand nits to pick. But if in fact somehow the string of words you put together creates overwhelmingly, repeatedly, with lots of different readers the same issue, then you ... I don't like notes of clarification I frankly would say "so edit it. Take it back and fix it".

Others in the authorship team did not seem to think that the term population would provide interpretive difficulty, such as:

A6: It is "populations" isn't it – in which the research is carried out?

In terms of interpretation of this paragraph the phrase "stands to benefit" sits alongside population as a key statement. In terms of populations "stand[ing] to benefit", it appears that there are two broad approaches. The first sees this paragraph as requiring a predictable benefit to the population in the circumstances that apply at this moment in time – for example, if a new treatment is shown to be beneficial and safe, a license will be sought, the treatment will become available for physicians to prescribe and the population will benefit. The second approach suggests that this phrase can be more imaginatively applied – i.e., if something as yet unforeseen and

perhaps unforeseeable were to happen then it is possible the population will "stand to benefit". This is well-illustrated in the following author's views:

A13: ... in particular you can have a number of interpretations about what "stand to benefit" means. It's arguable that the population of sub-Saharan Africa stand to benefit in ways that may not be immediately apparent by advances in our understanding of the treatment of AIDS. It may not happen to them tomorrow or next week or the year after but you know who's going to say that benefit to the people that followed them 5 years from now wouldn't be worth having.

RC: So serendipitous benefit that you can't predict also somehow needs to be recognised?

A13: I realise that that's kind of weaselling around this in a way, but it's real. And I think as an aspirational principle, that's pretty good aspiration isn't it?

As an example, perhaps, of an outlying view another of the authors used a specific illustration to make a point regarding interpretation of Paragraph 19 requiring fairness within communities where research sponsorship raised the level of care of some in the community but not others. The example was a developed country sponsorship of a trial of surfactant in neonates in a developing country. As part of the trial the general standard of care of the neonates was raised to the standard that would be delivered in the sponsor's own developed country. Quite remarkably perhaps, this author used the illustration of a parent with 2 children finding a beautiful doll

A5: You have 2 solutions ... you must now share the doll. But they can't understand that, they are not accustomed to that - at the Christmas before, they had 2 dolls. Not a good answer or...

And the interviewee went on to say that giving only one of the children the doll was also not a good solution so the answer is not to give the doll to either. Using this analogy, the assertion was that the surfactant trial should not have taken place because the improved general standard of care wasn't being offered to all. This was used to assert that, once the NoC30 had been finalised, that Paragraph 19 should be subject to a Note of Clarification.

Another found concern with the "strong" versus the "weak" interpretation of the requirement for "reasonable likelihood of benefit"; the strong interpretation requiring the prior demonstration – in a convincing way – that benefit would accrue whereas the weaker interpretation would be that a hypothetical chain of events that was not too far-fetched (i.e., reasonable) could result in a benefit accruing. This particular author concluded that the strong interpretation was probably not tenable stating:

A11: ...by the time you know there's a reasonable likelihood, the individual clinician is bound to have [done the] work – taken in advance of the ability to demonstrate a reasonable likelihood.

The explicit concern for research on vulnerable groups – both those vulnerable by virtue of their economic status and those vulnerable by virtue of their illness - were mentioned as implicit in the interpretation of Paragraph 19:

A2: ... the other background which is about this is about vulnerable groups. And so this expresses same thing that you don't do research with schizophrenia patients if the problem is not essential just for schizophrenic patients and that on the other hand this is broader that also that you don't do the frostbite research in Sahara but in [cold climate countries]. So that you choose relevant circumstances. And also what health care system that ... if the local health care is not capable of dealing with

that kind of laboratory test or x-rays or they don't have the technology in continuity you don't go there and that's what we call research exploitation.

And a further comment from one of the authors affirms again the question of the interpretation of the word "population":

A8: Of course, the question then would be how do you define population? Is the population a country? Is it an ethnic group?

This author went on to point out the importance of this paragraph in the context of research in vulnerable groups:

A8: ... then you have this kind of subject groups that are especially vulnerable so one of the things that's written is that you should research them only if you can't get the thing researched from another group that's not a vulnerable group. But does this also mean that this has to benefit them specifically individually other than part of a benefit to the general population so I think there is a lot of room for interpretation but I think that because I see this as a guiding principle, I think we should move in that direction.

Thus, while retaining the requirement that research should only be conducted in vulnerable groups when the research question addressed the issue that makes the research subject vulnerable (e.g., conducting a clinical trial for a drug to treat dementia at some point would need to be tested in that vulnerable population), this interpretation allows such research to take place in the absence of a "reasonable likelihood" of benefit to the individual research subject provided the benefit to the particular vulnerable population could be envisaged as reasonably likely. However, again, the notion – as discussed at length above – that the DoH contains "guiding principles" is at the centre of the interpretation issue.

A further issue that was raised by authors in relation to several of the interpretive difficulties was the possibility that a glossary should be developed to help with definitions of words such as "population". This received a mixed response from those involved in the authorship process. Such a mixed response is another window into the intention on the part of the authors (as discussed above) that the DoH retain a degree of flexibility in interpretation.

One example of an author in favour of a glossary:

A15: It's not how I see it. It's still not how I see it. And I couldn't see how in a world document any kind of reference to a health care system was going to work because even the words "public health care system" mean different things in different places so they're a meaningless set of words as far as I'm concerned.

RC: Again, the need for a glossary which you mentioned earlier.

A15: Yes.

And a case of one of the authors that thought a glossary would be counterproductive:

A4: ... the way we would describe in a glossary in quite a soft way was seen as a disadvantage and they felt that you know you raise even more questions if you try to define a population than if you actually leave people to define it for themselves. And because it's meant again to be guidelines, the question asked 'well the people should actually define it for themselves'.

Further comment by those involved in the authorship group indicated the WMA did take the beginning steps to commission a glossary but then decided against the step and the process was, at the time of interview, not continuing.

Medical Researchers

A key observation with respect to the interpretation of "population" is illustrated by the following:

MR15: ... Clinical research is only justified in these populations that are likely to benefit from it. What does it mean? Does it mean that if you want to investigate a rare disease in African or Caribbean populations and then you ... does it mean you can't do the research in Japan? Does it mean that you can't have Caucasians in North America joining the trial? Because the other populations to benefit? Or conversely, if you want the Caucasian population in Canada to benefit from the trial, does that mean you can't include Africans in France? Or paediatric trials, and conclusions to adult?

As will be seen below, this kind of observation tapped into a strand of interpretation that the authors perhaps had not intended – as illustrated by the subsequent modification of this material in the 6th (Seoul, 2008) revision to explicitly allow for the type of research to which MR15 refers above.

This same researcher made further mention of the difficulties with interpretation and application of Paragraph 19:

MR15: No, no. I think the reason I haven't seen this is because we're involved with mainly .... main ... mainly ... this is patients ... clinical trials with patients. Sometimes phase I volunteers, but patients. And patients usually have the same disease that you are looking to cure. So there is no reason ... you should ... because if you look for a psychiatric drug then you look for a psychiatric patient with the same disorder, (indecipherable) you are targeting so there is not much issue. But I think this will become more and more of an issue, the more genetic research advances. Genetic research is targeted specifically. They target populations ... and they are going to tailor, try to tailor, the drugs because you and I, our bodies don't respond the same to the same usage.

In some cases, medical researchers simply articulated their struggle with definition

and interpretation:

MR1: I'm afraid uh ... This ... sentence could be interpreted in various ways. And uh ... I believe that population is not specific territorial population ...

One issue that was raised by authors in their concerns about "reasonable likelihood of benefit" was that, in some cases, in research in resource-poor countries a license for the drug was not even going to be sought because the returns did not justify the administrative effort. When raised with one of the medical researchers, the following interpretation was stated:

MR3: Yeah ... my assumption is that if they thought the drug wasn't going to be produced for use in that country it probably doesn't meet the test. And that they're referring to the general population not the people in the trial, in 19.

One particularly interesting – but lone view – articulated by the medical researchers was a concern that the requirements of Paragraph 19 may come up against equivalence studies. If a "me-too" drug was being developed, how could that be seen to benefit the population?

MR7: ...It would call into question all kinds of things like, for instance, companies researching "me too" drugs. And the whole principle of equivalence studies for instance. Where would the benefit be for populations in equivalence? Are equivalence studies unethical? ... So I think one should argue certainly that research should only be done where there's a reasonable chance that it will benefit mankind if not the individual patient.

RC: You're interpreting "population" as all of mankind?

MR7: Yes.

In terms of the "strong" vs. "weak" definition of population, this latter view is as weak as it gets! (For arguably the best presentation of the definitions of these terms as they are being used here, see the comment by EC8 in the next section.)

We see the difference between the "strong" interpretation of reasonable likelihood of benefit and the weak interpretation in the following comment (that fits squarely with what is defined here as the "weak" interpretation):

RC: ... if someone's income is one US dollar a month and you're going to develop a drug that will cost them a thousand US dollars a month and no-one's going to develop a subsidy, don't pretend that that will benefit the population.

MR5: And what I was saying to you is the only circumstances where I think you could argue that is if you could foresee that in 5 years' time when that drug is off-patent and it now costs a dollar that it would be available. So that's what I was meaning about taking the longer term view. It's quite important to look at what the drug would cost because some drugs are always going to be expensive because the manufacturing is expensive. Some drugs are expensive because they're the first drug but you go down the line when you've got the next and the next and the benefit might be available.

One of the medical researchers interviewed commented, in relation to interpretation of the phrase "reasonable likelihood" that "the wording is fine" but then went on to give a very broad interpretation of the notion of "benefit":

MR8: ... the people participating in the trial can benefit from the result in many ways. I mean (a) the result may influence what their government chooses to do in the reorganisation of their health service and the provision of whatever it is and (b) the results may have a wider spread impact in that various regimens of monitoring may come to be standard. And that can go both ways. I mean it may mean more frequent monitoring or less frequent monitoring or it could be a different method of administering a treatment that not only applied to the treatment being tested but to other things too. And the trial might have initiated a change in health care delivery

in some way or another which could then become part of standard practice if it was deemed to be better. So I think there are many ways in which the benefits of the results of the research could be applied to the group.

The notion of "benefit" incorporating the improvement in the evidence-base for public health decision-making for the population in question was not something raised by any of those involved in authorship. Yet the words themselves seem to allow for this view.

It is interesting to see how this researcher continues with interpretation of the implications of "reasonable likelihood":

MR8: I think it always hinges on 'reasonable likelihood' which again comes back to my point of the discussion at the beginning. If a sponsor and a government are comfortable, both of them comfortable with a position they've arrived in at the initiation of a research project in all aspects like this, it's very difficult to justify that the research shouldn't be embarked on.

The locus of decision-making as to whether the population's interests are satisfied is located, in this researcher's view, with the government. Arguably this is acceptable in a democratic system because the government is ultimately beholden to the population. However, the adequacy of protection for the population could be called into question in an autocratic system. Even in a democratic system, if the population affected by research were not sufficiently large to wield enough political power, and the interests of the particular population are, for whatever reasons, not championed by larger sections of the community, it could again be questioned whether this interpretation gives adequate protection.

Expert Commentators

One of the commentators picked up on a grammatical concern regarding the wording of Paragraph 19:

EC18: I wish they wouldn't put their 'onlys' in the wrong place. I mean they've done it all over the place; 'medical research is justified only if ...' not 'only justified if'. But never mind, that happens so much in English these days. It's one of the many ways in which English is massacred, yes. So this is saying you can only carry out medical research where the population who are being researched upon could benefit from that research. So if there's no prospect of them benefiting ... so you shouldn't do diseases related to mosquitoes on Eskimos. I mean you shouldn't research a drug for ... that's a silly example isn't it? You shouldn't whatever ... you should ... not only that there is, the research is relevant to this group and the research is also going to result in some benefit to that group.

Another of the commentators had a unique and interesting point to make with respect to "reasonable likelihood of benefit" to a particular population seeing research as having a broader "beneficial" remit than that.

EC20: Reasonable likelihood ... you can imagine a whole committee on that one. Well it makes a very ... it makes research a very goal-oriented undertaking where the goal is to provide beneficial results rather than to provide information. And it think to that extent it's actually a little bit narrow. One would hope that the majority of effort in medical research would be towards these things but at the same time I think finding out for finding out's sake can be important because who knows later what might turn out to be important, what might turn out to be worthwhile? What I'm saying is that I don't think there's anything wrong fundamentally with simply gaining information even if you know that there's not going to be a benefit there. Where the wrong comes through is how you go about gaining the information, right? Obviously what you need to do is ensure that whatever information is gained there's going to be people who are willing to assist in this gleaning not from people who are being treated merely as slabs of meat or as research objects.

The same commentator also applied interpretation of "only justified" in a logical sense as a necessary condition:

EC20: So, on the other side I just see it as problematic in saying what it means.

RC: How so?

EC20: Well just 'is only justified' ... 'only justified' from a philosophical point-of-view that makes it a necessary condition, only if there's a reasonable likelihood so you say if there isn't a reasonable likelihood, whatever that may mean, it's not justified. Reasonable likelihood is usually something that arises as a result of research. Determination of likelihood - so in that sense it's too narrow because it's going to be self-defeating. So you've got no other provisions going to be something more prescriptive and so that medical research is encouraged where there is a reasonable likelihood ... rather than saying it is only justified or alternatively go the negative side and say that 'medical research is not justified if it both is merely for the purposes of gaining information and will, incidentally, afflict pain and suffering on people'. So it's either going to be a ... the 2nd one's called a defeating or defeatability position and the 1st one being prescriptive ... rather say that it's to be encouraged.

Another of the expert commentators also developed the notion of a "weak" interpretation and a "strong" interpretation, and both the notions of "population" and "reasonable likelihood of benefit" had weak and strong version. In fact, this commentator applies an even stronger interpretation of "reasonable likelihood of benefit", requiring for the "strong" definition a prior negotiation of the actual pathway to benefit for the population.

EC8: ... there is a weak interpretation of this and a strong interpretation of this. The weak interpretation ... the weak interpretation simply requires you to demonstrate ... in order to interpret this it requires you to demonstrate that the research is relevant to a health problem in that country.

RC: So you're interpreting population as a country?

EC8: Well, I am here.

RC: Okay.

EC8: I am here but it's a good question. I am interpreting this as a population as opposed to the sufferers of the disease but then I don't see any way of interpreting this to mean research is only justified on AIDS people if people with AIDS will be benefitted because you wouldn't do research on AIDS with somebody who doesn't have AIDS. So this is, if not a country, it could be poor people. It could be a region. ... So in saying there's a weak interpretation I mean it's going to be either people in resource-poor countries ... I don't mean ... I mean suppose you're looking at river blindness or you're looking at parasites that are in people in poor countries. There are two different scenarios here. One is you go in and do cancer research in some ... I don't even know if the infrastructure ... but you do some really high-tech thing that requires a medical mecca essentially and you know that in Botswana they're not going to ... in Mali they're not going to ... be able to implement something like that. And that would be a case in which the benefits would go to the north because people have cancer in all these different places. So I mean, one way of interpreting that is "don't go and do cancer research just because it's cheaper to do it there if there's not a chance in hell that you're going to be able to provide what has to be provided to provide the treatment eventually. Even if you could set up an elaborate infrastructure just to do the trial" ... which is unlikely that anyone would want to do that but it's feasible. So ... but the weak ... I said there was a weak interpretation and a strong interpretation. The weak interpretation is to interpret this only as meaning that the disease has to be a prevalent disease in that country. It has to be responsive to the health needs but without requiring any interpretation of reasonable likelihood. The likelihood is that they would stand to benefit if ... if what? If the government would pay. If something else happened etc. So the weak interpretation is – another way of phrasing this that appears in other places is "research should be responsive to the health needs of the people". And, as long as it's responsive then it's anybody's guess what the degree of likelihood is and you'd have to look at those conditions. ... A strong interpretation, which I don't know if it was intended, or in anybody's mind is that, there should be some form of negotiation, prior agreement, arrangement or preparation to make the product available and not just go in and do the research and say "oh okay we've done the research, now what are you going to do about this and who's going to do something about it?" So the whole concept of prior agreements that are forged in some way among the researcher, the sponsor, again the Ministry of Health and anybody else who can get into the act to see that the successful products of research are made "reasonably available" because that's what CIOMS says that it should be made reasonably available. This says a reasonable likelihood that they stand to benefit ... that's different from saying that the successful products of research should be made reasonably available. So it requires a lot of interpretation to know just who has an obligation to do what. And who has an obligation to do what, when? In order to put some teeth in this ... again

it would have to be some consortium not just the lone researcher – I mean people objected to CIOMS by saying, researchers? What kind of power do they have? I mean they're guys who work at ... I mean they don't even have the skill, I mean they're not PR people, they can't do this. Well, of course, the researchers aren't. But as we know from PR and publicity and advertisements there are plenty of people who have the skills and can do all of that. So this is too vague and one can imagine virtually anything if this had to go before an ethics committee. One could imagine the weakest possible interpretation of this: both 'reasonable likelihood' and 'stand to benefit'.

Another of the commentators, having given the matter some prior thought (as evidenced by reference to "making a note") saw some definition of "population" as being essential to the interpretation of Paragraph 19:

EC19: I've written a note here and highlight the "population" – how do you define "population"? What population are you in fact speaking to? The limited population of the people you are treating? Or looking specifically at the Masai tribes in Africa?

RC: Would you accept, as a valid interpretation, as the group of people who could have been subject had they been selected as part of, say, a randomisation procedure?

EC19: No, I think that the distinction that you want to make is whether the population in which the research is carried out means that population they speak of and people identical to them. But is it that narrow interpretation or is it a wider interpretation? Would it be – could be for the country so to speak?

RC: Or all of humanity?

EC19: The only note I've got there is that somewhere or other it would be nice, and better, to define population.

Another of the commentators, voicing views on the interpretation of "population", suggested that it was not a very clear term but that there probably wasn't anything better. After grappling with the issue of the meaning of "population", and how much

latitude could be given to the term "population", this commentator's initial interpretation of the wording of Paragraph 19 was:

EC16: ... I would interpret that in doing research on a condition which or for ... I mean it could also mean for the drug which is always going to be out of reach. So don't conduct high-cost drug being researched in Zambia who are never going to be able to benefit from that.

Another interesting interpretation espoused by one of the expert commentators [EC3] was that Paragraph 19 also carried within itself an obligation to do focused research – often on relatively small "populations" – such as with the development of what are sometimes known as orphan drugs or the need to undertake research in children where the methods are intended for use in children.

Many of those interviewed saw Paragraph 19 and Paragraph 30 as interconnected and this was also the case among expert commentators. There was also often a tension between the various disciplines represented in terms of their interpretive approach to the DoH – expressed in a somewhat "tongue-in-cheek" manner in this statement but generally carrying some serious undercurrents for the task of interpretation.

EC5: That's what happens when you get the lawyers into a problem. It's it would be the case that it's accessible just as it could be the case that there exists proven therapies, just not available here, um ... it ties into the other debate which was happening about the same time to do with access to essential medicines and um ... intellectual property regimes and trips and so on ... and I think you have to take it in that context and I think that um ... the issue of what the responsibilities are of national governments, international organisations like the WHO, NGOs, pharma corporations and so on, where responsibility lies for delivering on Articles 19 and 30,

The interpretive difficulty was over what the definition of "access" was in Paragraph 30 and the related issue of whether there was a "reasonable likelihood" of benefitting the population. The same interviewee, taking the overlap of Paragraphs 19 and 30 and the interdisciplinary difficulty with interpretation further commented:

EC5: ... if you take the document as a kind of logically coherent text, then you have to follow the logic where it leads, don't you? And there isn't a kind of ... the WMA, for example, has the Declaration of Tokyo about torture and various other Declarations and so on. It doesn't fit very easily either into an international politics which tells us how to or ... order these things or into an international jurisprudence that would give us a canon of interpretation.

These comments are very illuminating in the context of this particular study where there are no specific "canons of interpretation" for a set of normative ethical guidelines. It cannot be exegeted in the same way as legislation or scripture.

What does govern all interpretation of texts is that interpretation of parts of the text takes place in the context of the whole of the text. Further, interpretation of any set of normative ethics requires a reflective equilibrium between the norms expressed in the text and the actual cases, the actual research scenarios to which they apply. This will be addressed more specifically in a later section.

Another of the expert commentators, in discussing the issue of "benefit" to healthy volunteers spontaneously raised both the issues of the "time" dimension to benefit and the "social network" dimension to benefit:

EC11: Well I think that throws us into the issue of what does 'benefit' mean. Because if you mean by, and that's also what I meant by when I said there's no time frame, because if you mean immediately benefit – well that's true. But you could even say that about some therapeutic research. I think that the question here as far as healthy volunteers is let's talk about benefits in relation to their interest particularly as regards their basic needs satisfaction in the longer term.

RC: So altruism and also the fact that they may develop the condition under study.

EC11: But not just them. You know we're essentially social beings. And so they may benefit in a huge number of ways because not just they may develop but you know the people on whom they depend, they love etc.

Another element that came up in terms of interpreting the "reasonable likelihood of benefit" was the benefit that may come to healthy volunteers if they are remunerated for participation – an issue on which the DoH is silent:

EC17: And similarly, you know, were people going to get paid here, of course if they're being paid so much that they will take risks that are against their better judgment, then it's a bad thing. But that as a criterion, and also the initial thing, which again is not in this guideline as far as I'm aware but is in the CIOMS guideline, is that the risks, the additional risk, should be minimal. So that you know, there's a protective criterion from the designers of the research as well as from the Declaration.

RC: That's interesting because the Declaration is otherwise silent on that issue...

EC17: I don't ... I don't think. No I was moving on from that to the question of payment. But the notion is that there could be some benefit.

RC: And that could include payment?

EC17: I can't see why it shouldn't include payment. I doubt very much whether it's intended to include payment, but I can't see why it shouldn't.

Finally, the following commentator echoed the views already mentioned in the medical researchers group, that a strict interpretation of Paragraph 19 would seem to preclude research on conditions prevalent in the developing world being conducted in the developed world.

EC5: Which was that you could have a ... you could get into trouble with article 19 if you wanted to do altruistically motivated research on tropical diseases in countries where tropical diseases are not endemic. So if you wanted to do research on river blindness in Oxford with healthy volunteers, you might argue that no-one's going to get river blindness from the Isis, so you should ... article 19 might imply that you shouldn't do such research in Oxford. I think that would be an adverse interpretation of it.

Interestingly, as shall be seen in the discussion of the 6th (Seoul, 2008) revision – see below – this concern seems to have been a major focus of the changes to this material in the 2008 revision of the DoH.

6.3.4.2 Paragraph 19: Research on healthy volunteers

Concern was raised in the early stages after the adoption of Paragraph 19 that certain interpretations of the word "population" combined with a strict interpretation of the requirement for "reasonable likelihood of benefit" precluded research among healthy volunteers including most phase I trials. As discussed above, there was talk of a Note of Clarification to this paragraph to settle the issue but this was shelved. In the final analysis there was not a great deal of difference between the conclusions of the Authors, Medical Researchers and Expert Commentators and the views are presented together.

A6: ... the whole foundation of this Helsinki may seem a little bit patronising. It seeks to protect the patient not to protect doctors. And it's just trying to get the doctors to behave in a certain way. And this was really that populations shouldn't be exposed to risk when there's no chance of them benefitting from it.

For the potential to benefit to really get to zero, a research population would need to be chosen that was completely beyond the realm of potential benefit. A phase I trial of a drug intended for endometriosis that included males might be an example. However, benefit to one's spouse, or mother, or sister through development of a new treatment may also fit the requirement for potential benefit. Some of the respondents seemed willing to stretch the definition of population to the entire human population stretching into the future.

This is well-illustrated in this dialogue:

A7: Well, unfortunately, our status today changes on a regular basis and today's healthy volunteer is tomorrow's recipient of health care.

RC: So the concept of population has that time ...

A7: Absolutely ... absolutely.

RC: Right, I guess that's what I was starting to explore is what you had in mind when you said population. Is it population of a country or is it a much more flexible concept than that?

A7: I think it is fairly flexible but I think the specific discussions had to do with the fact that again you don't subject people to risk from which there is never any intention they would benefit okay. But we all know, of course, that we must have healthy volunteers for some of our research otherwise we simply couldn't advance the healthcare process.

And finally, there were those in the authorship group bluntly dismissive of even the possibility of the Declaration suggesting that healthy volunteers somehow were either excluded from research or offered a lesser standard of protection by the DoH:

A11: Oh rubbish. Total rubbish. The only distinction between healthy volunteers and patients is there's no way a volunteer can possibly benefit from it other than perhaps feeling good about doing it or having generous expenses helping them to finance their studies or both. Whereas theoretically the patient may benefit from this ... I don't think it matters a damn, whether it's to do with a patient or a healthy volunteer. Because the same ethics are applied to both, the same care, the same consideration, the same very very careful monitoring of the whole thing to ensure primum non nocere.

Although most medical researchers did not take issue with Paragraph 19 being interpreted as excluding research on "healthy volunteers" this was not always the case:

MR2: Taken to its limits of course, it pretty well crashes volunteer studies 'cause healthy volunteers aren't going to benefit so if it could include that then it would completely make a nonsense of volunteer studies 'cause ... Now you know people do when they do volunteer studies and they say 'we'll conform to the provision of the Declaration of Helsinki'. In which case, this Paragraph 19 becomes a no-no.

It is interesting to note the bidirectional conclusion involved in this interpretation. On the one hand, the interviewee comments that taken literally healthy volunteers research is excluded. However, the final comment is that "Paragraph 19 is a 'no-no'"! This touches upon our study of Paragraph 9 (see below) – the authority of the DoH (and by extension the authority of the WMA). However, this interpretation certainly resists such authority and sees the WMA as being in the wrong by including the paragraph as it is worded.

Another medical researcher appealed to the unknown future as a justification for "reasonable likelihood of benefit to the population" after initially raising a concern that it was a "semantic" quibble:

MR19: Well it's a little bit semantic isn't it?

RC: In what way – because semantics are important aren't they?

MR19: In the sense that there are a lot of diseases that all of us can suddenly get, even if at the moment you're a healthy volunteer, nevertheless you can get ill, and therefore this would allow you to involve everybody. The only place where we have this statement is in studies with children.

Presumably a case could also be made for including other vulnerable groups besides children in special exceptions simply so that they do not become "samples of convenience". However, the point is clearly made – population must be interpreted to include future patients. It is interesting that none of the interviewees, in this group or any other, mention that a healthy volunteers friends, family or others that are important to them (perhaps even favourite actors or sportspersons!) may have or develop the condition that is the focus of healthy volunteers research. Might this also be considered a benefit to the population?

Finally, it is interesting that the "term" semantics – which essentially is the study of meanings of words, should come under fire in a discussion about the interpretation of a text. It could be argued that what is under fire is "pedantics" (or perhaps, more correctly, "pedantic semantics") rather than "semantics" *per se* – the latter of which is fundamental to any discussion of the meaning or interpretation of a text. Semantics profoundly changes lives, changes economies and is at the heart of international diplomacy if nothing else. In a global document such as the DoH, it should not be surprising that semantics is of major importance.

Another commentator agreed that a strict interpretation may preclude research on healthy volunteers but then equivocated. The dimension of time might always allow for such research in that healthy volunteers may in future develop the condition that is the focus of the research:

RC: Well others have said if you take this to its extreme it excludes all healthy volunteer research.

EC18: Because I mean it would yes. I mean if you're going to read it that way then it would exclude all phase I and healthy volunteers since you know ... well it makes a question, it depends what you're trialling of course. If you're trialling something for hepatitis B or something you know and they might get it sometime later in their lives, they might not. Yeah, I don't think you can read it that way. I don't think you can read it ... I think there has to be ... there have to be some aspects of research with people who themselves are not ill that go by different rules and I think would be the first thing I'd say. Otherwise you would have to take healthy volunteers out of research altogether and if you did that it would be very very difficult.

Another of the commentators agreed with the view that Paragraph 19 does, with some possible caveats, appear to preclude research on healthy volunteers:

RC: ... this would appear to suggest that healthy volunteers should not be used.

EC13: Of course, that's true. But I really hadn't thought of that. You're absolutely right it does seem to suggest that only those who are likely to have a benefit can actually participate in it. It also would seem to rule out ... I mean it would also rule out what in old-fashioned terms we used to call non-therapeutic research which goes beyond healthy volunteers obviously because it does seem to suggest that only where there is a benefit ... of course that may be why they've got the word 'populations' in ... This is sort of like Adults with Incapacity stuff again. So if for example you wanted to conduct research on children which would probably be one of the more contentious areas and the research you needed to do involved children who were not ill, then I suppose this would actually allow you to do it oddly enough because it talks about the populations benefiting and presumably by population we could mean the category of child as opposed to individual, as opposed to individual children so I suppose there is an argument that in fact you could include anybody in it including

healthy volunteers because they merely form part of a population identifiable as 'boys' or whatever. But at first sight it does appear to suggest that only people who could personally benefit in their ... well the other thing of course is they don't actually explain what they mean by benefits. Well I could argue that being paid fifty quid to go and be exposed to the common cold is actually of benefit to me and I suppose that that wouldn't preclude. I mean they don't say whether or not they're talking about a physical benefit or a financial benefit or a psychological benefit from participation which means its just another piece of flim-flam typical of the Declaration of Helsinki.

So this last commentator dismisses the argument against research on healthy volunteers not by virtue of argument from within the text but by being dismissive of the DoH as a whole. However, by and large, the tenor was that either Paragraph 19 did no such thing (that is, discount healthy volunteers research). Where it was conceded that, on one reading the text might exclude healthy volunteers research, commentators either dismiss that as the intent of the WMA or dismiss the validity of the document altogether!

6.3.4.3 Summary

In bringing together the various interpretive comments with respect to Paragraph 19 it seems that the phrase "reasonable likelihood of benefit" broadly falls into one of two categories. The first is benefit that is foreseeable without any need for an unforeseeable change. Once the method under research has been proven beneficial, the existing mechanisms are likely to make the vaccine, the diagnostic test or the drug under development available to the population and the proven benefits would normally be expected to be achieved.

Others, however, were willing to countenance a benefit to population that could occur if something else – as yet unforeseeable – were to take place. This could take the form of a philanthropic intervention, either through international aid or private donors, making an expensive intervention available in a resource-poor population. The unforeseen change could even involve an unexpected discovery of resources – oil, valuable minerals or the like – changing the socio-economic status of the population and making expensive interventions now within reach. The key definition here, however, is that the change is theoretically possible but as yet unforeseeable. The degree to which this paragraph restricts the conduct of research on resource-poor populations thus hinges around whether such "possible but unforeseeable" changes constitute a "reasonable likelihood of benefit".

Regarding the variety of interpretations with respect to "reasonable likelihood to benefit [to populations]" there seemed to be little support for the "strong" definition described above (again see comments by *E8* for a thorough definition). Most, if not all, from the 3 groups countenanced some "weakening" of the definition or at least some "elasticity" in the definition. It can be seen through the comments that such "weakening" or "elasticity" can be achieved through interpretation of the term "reasonable likelihood" or the term "population" or both.

With respect to the issue of research on healthy volunteers, all of the interviewees seemed to be interpreting the text in a similar manner. "landscape". There is broad

agreement that the effect of Paragraph 19 in no way precludes healthy volunteers research. Yet, there was evidence of such great concern at one point that one of the authors mentioned that a Note of Clarification had been mooted (but subsequently dropped). This thesis has already suggested, in Chapter 4, that such an interpretation (preclusion of research on healthy volunteers) represents "deliberate decontextualisation and misinterpretation of the intent of the paragraph".

6.3.5 Paragraph 27: Publication

There was broad support for the changes in the 5th (Edinburgh, 2000) revision in the material relating to publication. However, a key issue in interpreting this paragraph related to what was meant by "negative" results. Further interpretive phenomena were observed around the phrase "publicly available".

Authors

An insight into authors' thinking about "publicly available" is provided by the following:

A15: ...I think those words were put in to take account of the new context of publishing ... that is to say – it's the Web. It does not mean published in a journal it means made available publicly on the web in a way that was accessible.

However, there was a potential "sting-in-the-tail" relating to this plan – the sheer volume may overwhelm anyone attempting a systematic review of the complete data available. As the same interviewee acknowledged:

A15: ...In much the same way as the public accountability agenda in government today is partly met by the fact that we just publish everything. We just stick up the minutes of the most arcane meetings and the minister replies [to accusation of concealment of information] ... "no we're not. We're making it publicly available. You just didn't ask".

It is important to hold this thought as the responses of medical researchers to the change in publication requirements is discussed.

Interpretation of the term "negative" was clearly giving rise to some interpretive difficulty. Some of the authorship team felt the emphasis was clearly on a requirement to disclose adverse events:

A9: we meant all results ...but the emphasis was definitely on negative as in adverse events.

A further comment strongly indicating that it was perhaps "adverse" rather than simply equivocal results that were envisaged in this paragraph was as follows:

A12: Well, my understanding was that it was um ... the former, that it was to try and get people to disclose when things had actually gone awry um ... and not bury that. And that um ... that there was a concern that unhelpful research could be repeated endlessly or repeated in different countries and that people could be harmed even though there would be a kind of memory somewhere that handn't worked the last time. It could expose participants to unnecessary risk um ... or or at the very least futile interventions because they'd already been shown to be not not useful in another context.

Medical Researchers

Interpretation of the term "negative results" was not clear-cut in the eyes of many of the medical researchers. Consider:

RC: Just to clarify some have interpreted this to mean that 'negative' as in 'adverse' results should be published, others have interpreted it more broadly as 'negative', i.e., 'no difference was found' ...

MR9: I think both ... both should be published. Yeah, but do you really want to read a journal that says, you know, "this drug which we thought might be good is no good"? Is that good reading? It's a very difficult value call to make but editors don't think it is. You know "shock! Horror! Dog did not bite man! Man did not bite dog!"

RC: Does publicly available necessarily mean publication in a journal?

MR9: I suppose not. I mean the Cochrane collaboration are a repository of trial results. ... A registry of trials, and a registry of results, and publicly available data ...

This same researcher went on to articulate an issue that was seen as complicating the requirement to make all data publicly available (for example, through a register of clinical trials):

MR9: ... are they publicly ... do they belong to the public? Who do they belong to? I went to a trial meeting recently. The meeting cost two and a half million pounds. It was just an interim meeting. They have 3 a year for one trial. Who owns that study? Is it public? Is it hell. It's the shareholders. And having spent so much money on that they ain't going to give it up – their IP [intellectual property]

Another of the medical researchers saw enormous practical difficulty in implementing the "publicly available" requirement:

MR16: Well it's pretty difficult to compel anybody to publish anything. I mean if you think of other walks of life, other professions, just thinking about the legal professions or something, the proceedings are carried somewhere so they are there ... but not all the background papers. Even auditors' background papers are kept without being published. And they're kept for scrutiny if you like and if they're shredded then the governments don't like it. They should be kept for scrutiny but whether you should publish them ... you can't force people to publish things. I mean I think a proper policy on authenticity and storage is good.

And further pointing out:

MR16: Well, making it publicly available doesn't mean it's findable. There's likely to be such a huge amount that it would be impossible to find it ... I think it's important that ethics committees do make public their reports; so they say "we reviewed these 12 studies and there was this toxicity for this drug and so on ..." ... the confidential ... I don't think you can force people to publish data ...

It seemed also that, in the case of this researcher the more natural interpretation of the word "negative results" was "adverse events" as those were the examples given.

However, when specifically asked:

RC: I gave that ... uh well some have interpreted negative as being adverse as well as no difference ...

MR16: Correct, I was thinking more of the no difference. If the drug's not going anywhere. If it's kicked and they go on to a follow-on that they are taking through and it doesn't have that safety issue I don't see why they should be obliged to publish it anywhere. It would be very difficult to enforce and I'm not sure about the benefit.

The discussion proceeded as follows and is reproduced fully because it provides an interesting insight into certain lines of thinking among medical researchers:

MR16: I think the ethical bit is satisfied by the committee itself publishing its annual report and saying 'I have reviewed that' so from a safety for volunteers or safety of the operator and the process we have that fulfilled. But for that one individual molecule that just has ... if it killed a group of people its going to come out anyway but it shouldn't do, that shouldn't happen. In the modern world that shouldn't happen. If it had given a few headaches or postural hypotension which is common and it's not going to go anything further who cares?

RC: The people who argue strongly for this say 'if somebody did develop that or a very similar molecule in future and tried it and further people got headaches and postural hypotension they could have certainly an ethical grievance against the fact that it wasn't published and therefore they were also exposed to this discomfort when it was already known out there in the human consciousness somewhere that this molecule would cause that'.

MR16: I think that's unlikely to happen in drug development because people are unlikely to come up with the same molecule. I think its likely to happen in some

academic type of research with people making the same mistake if you like, like giving morphine and they get sick. That must happen all the time in clinical trials and even when they know that morphine causes vomiting if you use it then patients vomit in clinical trials. I think it's just an impossible one to cope with.

RC: I just am exploring it because your views on this from the practical perspective you have are very important so it's not that I'm expressing disagreement.

MR16: You want to publish and make available data that are helpful, true and ethical. And to publish all that negative things like that I don't think will be helpful ...

RC: So your concerns about this are not so much about the protection of intellectual property – it's more just the practicality ...

MR16: I'm afraid so.

Expert Commentators

One of the expert commentators, in addition to interpreting "negative" in this paragraph as meaning results that did not "disprove" the null hypothesis as opposed to "adverse" raised a further issue that is not directly addressed by the DoH, that of the choice of end-points in research.

EC5: ... If you don't refute a null hypothesis, that is, for all purposes a negative results and uh ... should be published. ...So I think that's fairly straightforward, that's just shuffling one's feet. There is there another issue which I would like to mention in this connection which is to do ... well, there are 2: Firstly, there is choice of endpoints, which this Declaration says nothing about uh ... at all. Some of the end points - if you take the schizophrenia example again, sometimes you're talking about um... you've got some endpoints which are fairly meaningless as far as the patients themselves are concerned. They may be concerned about holding down a job or live at home rather than live in an institution. That's that's one issue. Or what your choice of surrogate marker is? Again, ... I think that's left to the scientific community to sort out which may be appropriate. The other one is what do you do about adverse events? Now, adverse event reporting is a minefield. And um... the this doesn't have a whole lot to say about things like: how do you run a data and safety monitoring committee? What principles ought to apply? Good Clinical

Practice guidelines has a little bit more but ... but still not a lot more. And how you report adverse events, to whom, and what format, and where you publish them are not really touched by this at all. So the sort of pharmacoepidemiological side of clinical trialling is really not handled very well by the Declaration. Even though it's pretty central to the other things they are talking about because what it's about is risk assessment for subjects. Later subject, we have more information about the risk, if not its benefits, than for early subjects. Disclosure of information to late subjects is a controversial issue.

The DoH leaves the issue of monitoring of studies to the ethics review committee (see Paragraph 13) and does not make reference to any separate committee for data monitoring. The DoH does, however, specify (Paragraph 17) the need to stop a study early where the risk/benefit ratio is seen to change, tipping the balance toward risks outweighing benefits or where such a clear-cut benefit is seen that the final result is beyond reasonable doubt. However, the issue of later subjects being given information about the earlier results of the study are not addressed by the DoH nor is the issue of the choice of endpoints specifically mentioned.

A further comment from an expert commentator drew again on the need for specific application on a case-by-case basis rather than a blanket requirement – while agreeing with the spirit of this paragraph. However, the lack of clarity as to the meaning of "negative results" also comes to the fore in the comments regarding interpretation:

EC11: I think that it again is such an abstractly worded sentence. I think that what would be appropriate, and it's not stated here, but I think it was the spirit behind it – what would be appropriate is for when IRBs or research ethics committees review proposals that some statement ought to be made about what the committee thinks should be published in relation to both of those possibilities. I mean it may well be the case ... the reason I say this it may well be the case – there may not be an a

priori answer to this thing. It may well be the case that there's some circumstances … Clearly there are circumstances where it would be highly important for negative results to be published as well as positive results. But I mean if we get into marginally negative results as opposed to dramatically negative results then I'm not sure it would be worth the candle. So unfortunately, for example, if they say 'dramatically negative' or something along those lines it would have been more helpful. I mean my problem again with this is not with the spirit of it – I'm behind the spirit of it – but I think it's the interpretation that's the problem. What I would suggest in a nutshell is that editors of journals should be encouraged where they in the process of editorial review they think that it would be publicly useful for .. and the review process usually will throw this up, they think that it would be publicly scientifically useful for negative results to be published then that should be one of the demands that they make on authors.

RC: Can I just clarify? Some have interpreted negative here as understanding it to be 'adverse, bad results'. Others simply have seen it as non-positive, i.e., they didn't show anything new. They just showed that this putative new breakthrough actually wasn't any better than the old one. How are you looking at the concept of negative?

EC11: In both ways. I mean that's why I said what I said which wasn't very clear.

The same commentator elaborated further his views regarding "publication of

negative results":

EC11: No, both ways. Because what I said was if the differences are marginal, if nothing really hangs on the publication …

RC: I wasn't sure whether you meant marginally negative as in 'they were a little bit bad but not too bad – minor side effects or something …'

EC11: What I'm saying is if nothing, as regards the protection of health is concerned, as regards the consequence being that it's the negative results not published say in relation to negative side effects, hazards, whatever, if those aren't given proper emphasis and therefore there would be a downside as regards the protection of health – then clearly they should be published. I mean anything that's obviously going to have a substantive downside as regards the health consequences of publication would entail publishing. However, in many instances this won't be so necessarily. All I am saying is that where an ethics committee anticipates this, then the ethics committee should make a statement about it. If they don't anticipate it and in the process of review it becomes obvious that this is so, let's say review by the journal, it becomes obvious this is so, which very often it would do, then the demand

should be that it be published and it should be seen as bad practice if that demand is not made.

Another of the expert commentators took issue with the alternative to publication,

i.e., being made "publicly available". The interpretive remarks emerged thus:

EC17: ... it seems to me to be a bit ambiguously stated. It doesn't state it should be published, it says it should be published or otherwise publicly available. And that really negates the objective. I mean I think the idea that negative results should be published is a very important one. I mean scientists have said for a long time "we need to know". And so have ethicists because if it's already demonstrated to be negative then to do this research again needs extra justification if it can be justified at all. But if it's to be merely publicly available, how are people to find out? I mean have they got to go to every ...

RC: How do you interpret the difference between published and publicly available?

EC17: Well I think that something could be publicly available in the sense that if you wrote to a pharmaceutical industry and said, "Have you done any research on ... whatever your subject is ... because we want to know the results?" Then they would be required to say "Yes we have" and "here are the results". But that would make it extremely difficult to know who to write to apart from anything else. And apart from all the pharmaceutical industries, what about all the medical researchers throughout the world? So it seems to me ...

RC: Publishing is a more active thing, publicly available is a more passive?

EC17: Publishing means it's there in the record, as it were, and you'd be able to go to, I don't know, to Index Medicus or some equivalent and look it up. This way, I think it's ... however it's a move in the right direction.

RC: It's interesting. I've not come across that distinction before that "otherwise publicly available" may have the effect of negating...

EC17: That's my interpretation. Again it may not ... but if I was reluctant to publish negative results, I'd say, "of course yes, they're publicly available, but I have to be asked for them".

This commentator thus makes the strong objection in this interpretation that addition of the alternative "or publicly available" negates the intent of Paragraph 27 with respect to publishing negative results.

This same commentator also lends credence to the interpretive view of "negative results" that it can possibly apply to both. However, on further consideration, the interpretation seems to equivocate, suggests that perhaps an additional term such as "neutral" may be more apt but then reverts to the view that "negative" can be interpreted as showing "no benefit" as opposed to active harm:

RC: Your interpretation of the word 'negative' in this context – I'd be interested?

EC17: Well I haven't thought rigorously about this but I take it it means you know, that some new agent that is hypothetically going to be an advance in treatment or … and a suitably safe class of treatment has however turned out to be not an advance in treatment or too dangerous.

RC: Well again I ask because some see negative as only adverse whereas others see negative as you describe as being "didn't show a positive benefit" so of less interest to publishers. And I was interested in how you interpreted "negative".

EC17: Yes, I suppose that if it didn't show a positive benefit, it's not 'negative' it's 'neutral'. But I think 'negative', from my own reading of it, I take negative to mean it wasn't beneficial.

Another of the expert commentators also focused the interpretive question around the definition of "otherwise publicly available":

EC14: As long as we understand what means 'publicly available' I think this is okay. … to me the results should be somehow publicly available in case they are needed. Keeping in mind that there are some confidential issues and you should respect the property rights. But the design of the study, for example, and the overall result, positive or negative, with some clarifications should be available. … Uh, it's well known that negative results rarely is any news so it's very difficult to publish

negative results in any scientific journal. I agree with that. But still you could have some publicly available ...

Another of the expert commentators clearly seemed to lean toward "adverse" in the immediate interpretation of "negative". This conversation occurred in the context of a discussion about pharmaceutical companies asking for "gagging" clauses in signing contracts with academic institutions:

EC21: Particularly in respect of outright negative results.

RC: As in adverse results?

EC21: As in adverse results.

There was some scope for "negative" to mean a type of result showing no difference between treatment groups, the use of the term "outright negative" (as opposed to simply "negative") in this context suggests an interpretation of the term "negative" as tending toward "adverse".

6.3.5.1 Summary

It seems there has been a broad agreement with respect to making all clinical trial data publicly accessible though with considerable disagreement about the practical issues as to how this should happen and some qualms about intellectual property. However, the really interesting interpretive issue here is surrounding the paragraph's use of the term "negative". Does it mean simply "negative" in a scientific hypothesis sense – i.e., no difference was shown between the null and alternative hypotheses?

Or does it mean "negative" in a broader sense of "adverse" or "bad"? In this regard, it is like the various groups are indeed looking at the same landscape but with blurred vision for some reason or another. There is broad agreement that both aspects should be included but a haziness as to whether the DoH in its current wording in the 5th revision can be taken to mean both.

6.3.6 Paragraph 1: Scope of the Declaration

Interpretive issues around Paragraph 1 centred on the question of what was meant by "identifiable" with respect to "human material or human data". There was also further discussion related to the impact that the explicit statement that the DoH would now apply to observational as well as interventional research has on interpreting the rest of the document.

Authors

There was some support among the authors for the concept of a separate document relating to research on stored data or human tissue, given that this forms a category of "observational" research and the issues relating to consent cannot be identical with those of "interventional" research (the starkest example being research on stored tissue or records of those who are deceased). For example:

A7: in fact I think [a further document is] not a bad solution. And I think would come back to what I said. This is broad brushstroke aspirational lines. Whether it's World Medical, CIOMS, or national legislation, there in fact are literally thousands of issues that this touches upon. And some of them deserve their own paper that says "touched upon here and here it is in some depth". Some of them deserve a more

legislative perspective guidelines, regulations, this is how thou shalt do it. … our tissue banks and others are really struggling with interpretation. I think what the intent is again as you've got to look at the difference between the constitution of the United States which is a few pages long and the libraries full of minutiae that attempt to apply that to every possible situation. This is best analogy the constitution.

Another of the authors, in discussing the decision to change the adjective used in the DoH for research from "medical" to "biomedical" also expressed a view that is highly relevant to interpreting the changes in Paragraph 1:

A2: So we wanted to broaden this one. We didn't want anybody to think that it ... that you follow these general ethical principles only with a living person in front of you but also when the patient is dead and you have his tissue example, you still then have to protect their information and the identity of the passed one. So I think that was a very much conscious decision. We wanted to change it.

Finally, one of the authors, although expressing some difficulty in recalling the intention of the word "identifiable" provided a unique interpretation of the thinking of the authorship process not reflected in any of the other responses: the inclusion of "identifiable" was for the purposes of validation of the source of data or tissue specimen and was not related to any possible issues related to confidentiality – and thus, also, should not be seen as being in contrast to "anonymised".

A14: The challenge I'm finding in my thinking is what did we intend by the use of the word 'identifiable'. …Meaning from if it's identifiable you know the source, you know the validity of the data itself. So it was for establishment of validity. …

RC: Okay. Just so it wasn't the idea that by being identifiable it posed a risk to the research subject that they may lose confidentiality or privacy …

A14: Not at all … it was … absolutely not.

RC: So the identifiable was that it could be traced back for validation purposes?

A14: Yes. And it was mainly ... you know now that we're discussing that would be the same language that I would use in terms of identifiable human data is that the material used for research is validated.

It is difficult to know what to make of the strong assertion of the definiteness of this interpretation as it does not fit with the interpretation of the term "identifiable" by any of the others involved in authorship and potentially entirely changes the meaning of this requirement. This interview, having taken place almost 4 years after the authorship discussionsmay, of course, reflect a failure to remember accurately the intent but this possibility could be applied to many other interviewees' observations. There is no particular reason to assume such an explanation as the basis for this outlying view except, arguably, the fact that it is so clearly different from all of the other authors' apparent understandings of the interpretation of this sentence in Paragraph 1

One concern, raised by some, about the implication for the DoH of explicit inclusion of data and tissue was the later statement in Paragraph 15 that research should only be conducted by scientifically qualified persons and under the supervision of a clinically competent medical person. The conversation with one author was illuminating in regard to the interpretation of this:

A4: It doesn't say 'by a physician'. That was a battle we fought to make sure it didn't say 'by a physician'. And medical can be interpreted in a way ... it can be used ... common usage in the [A4's home country] would be people working in the medical community who would be competent to do that research. So I would have no

problems with the [non-medically qualified] epidemiologist doing research on records. I would have a real problem with the epidemiologist doing research that involved administration of some complex technique or drug, but it's about people who are competent and who work within the medical community or the health community. There are one or two people who think it always had to be supervised by a medically qualified person ...

Finally a further insight into thinking among the authors was demonstrated in the following comment:

A8: Because we don't want to misconstrue and say 'well when you're just collecting the data because you want to get statistics, you want to get epidemiological information, you want to get things like that, we can't do them because of this' or this statement would put ... you obviously cannot give consent and you don't need consent if what you're doing is just let's say taking the information that's in the patient's chart and you're just aggregating and sending it off to someone to do it. So you don't want to hinder what is needed and that's why did it with identifiable. But on the other hand, the idea is to try to get all research in here.

It is difficult to escape the conclusion that this interviewee saw the inclusion of the word "identifiable" as "hedging one's bets". On the one hand, the final sentence seemed to indicate an intention to broaden the scope of the Declaration to cover "all research". However, this has to be placed alongside the somewhat contradictory observation that the inclusion of the word "identifiable" was intended to exclude certain types of research, namely, that which used anonymous patient records where the possibility of ever re-linking the data to the individual was removed. A generous interpretation of this viewpoint would be that there is a creative tension involved in this interpretation. A less generous interpretation would see this as confused thinking about the meaning of this paragraph – a risk that is ever-present even when experts are interviewed when they are being asked for their spontaneous recollections and reflections.

Medical Researchers

Some of those involved in medical research also explicitly spoke of the importance of interpretation of the term "identifiable" in determining the implications of Paragraph 1:

MR12: Well it will all hinge on interpretation.

RC: Where are the interpretation issues?

MR12: Well as soon as you use the word identifiable because culturally from a data confidentiality, data protection perspective, there are totally different interpretations of 'identifiable' even between say the U.S. and Europe. So again, and I don't know if those nuances were recognised and the view was that that's not relevant to construction of this particular concept but I've ... I guess one of the things that has prompted the inclusion of that was probably the Icelandic Decode ...

While providing insight into the interpretive process around the specific word "identifiable" as important in understanding Paragraph 1, this is also an excellent example of a more generable interpretive principle in this study. Those involved in the medical research endeavour lie on a spectrum of, for want of a better word at this point, *access* to the intention of the WMA authors in the wording of the DoH.

Expert Commentators

The issue of constitutional interpretation raises its head again with the observation of this expert commentator:

EC10: My comment again would be – you see if you have that kind of statement there and you have thoughtful people on an ethics committee when an epidemiological study comes up, they'll ask themselves 'what does that mean?' And then they'll grapple with the meaning of consent for some future research project. And then they'll come up with something that is culturally relevant, which is going to

work in their society with the consent of the people and ultimately... And again it's like the constitutional judges interpreting the constitution, trying to make a document play out in the spirit in which it was intended without asking for every 'i' and every 't' to be dotted and crossed.

Everything is at stake here – a proverbial can of worms is opened again. The DoH itself purports to give guidance to ethics committees but in this analysis is entirely beholden to ethical committees for its adequate interpretation. Everything depends on the virtuous interpretation once again. The difficulty, of course, is for the text – what kind of text does it become? All it has to do is raise the issue and then let the virtuous men and women of the "constitutional court" of the ethics committee deliberate their verdict. The question arises as to whether this is all that can be expected of this kind of text, that it raises the questions in a way that is taken seriously. Clearly if the text is so inane that it is not taken seriously it will not guide any serious discussion. However, are we coming up against some kind of limiting condition for any kind of normative guidance? It simply cannot guide beyond a certain, and quite general, point. If so, then, we must ask, where is the appropriate point to break off the struggle and accept that the text can only get infinitesimally better than it already is, and that miniscule improvement will only be gained at enormous cost in the time, effort and energy of those drafting the text?

A key interpretive feature in the English version of the DoH centres around what is meant by "identifiable". Already discussed above (Chapter 5) is the possible difficulty with the French translation "non-anonyme". The concern around the definition of "identifiable" is well illustrated in the following exchange:

EC9: Well, I think it turns on the word identifiable. If the term 'identifiable' includes coded materials I don't think that there's a problem. And so the real issue is do people confuse coded material with anonymised material? Anonymised material, quite frankly, I think the major issue with anonymised material is the pressure towards permanently anonymising samples or records which in the process then lose some of their potential value as research tools, rather than undertaking the more diffiult process of getting the appropriate permission from people and building in the safeguards that would reassure them that the information that is not anonymous although perhaps coded will be used in a way which will not harm them. And so the pressure towards anonymisation if it goes to the repository side rather than the individual use could eventuate in the destruction of information which would be useful if it were not totally and permanently anonymised. There are, of course, other sources of information and studies for which anonymous data are perfectly useful. Prevalence in the community, where you really don't care who it is, or what else about them, you just want to know 'what's the rate of something?' where the fact that data are anonymised or were initially collected in a way that was anonymous is not harmful to the research. ... I think that the predominant use of the word 'identifiable' today in research circles recognises that coded material is identifiable. It may not have on its face the identification but as long as there is a code that someone could have access to, whether the researcher or someone else, then the data could potentially be linked to a person and identified with them and that makes it identifiable.

One commentator used the intricacies of legal interpretation to suggest that

Paragraph 1, in mentioning "identifiable" tissue or data does not automatically

exclude "anonymised" tissue or data.

RC: Some have questioned ... the lack of inclusion of anonymised research.

EC20: It's not excluded though, is it? It depends. Again this comes back to the idea as to how you read. It just says that this is a statement of ethical principles to provide guidance in research involving human subjects. So it doesn't say that you know 'not equally to other things'.

RC: Right, well that's an interesting interpretive point.

EC20: This is where law has ... you go back to common law – it's got those two quite contradictory principles of law in difficult principles of interpretations. One is

expression exclusion altruis: if you say one thing and not the other, then other things are excluded.

RC: Right.

EC20: And the other principle of law for interpretation or canon of interpretation as it's called is: there's a 'and so on' interpretation principle. So you've gone on the basis where it's like enough, you carry on the same principle.

6.3.6.1 Summary

While there is broad agreement that the ethical dimensions around human tissue research and research on health data are important there is some disagreement that a document initially designed to deal with clinical trials on human subjects is the best format for dealing with these issues. If the views of *A14* are set aside for the moment (which, if correct, completely change the meaning and intent of the paragraph) there is some interpretative disagreement relating to the meaning of "identifiable". However, this is the only disjunction of interpretations evident. The major additional disagreements are whether the rest of the DoH (with respect to consent for example) have adequately accounted for this change or, indeed, whether the DoH is the place for dealing with this type of research at all.

6.3.7 Paragraph 9: Authority of Declaration

Perhaps surprisingly, this generated little interpretive controversy with one notable exception among the "Expert Commentators". The controversy was over whether the change in expression actually meant anything given that the DoH does not have any

regulatory status. The views of the three groups will be dealt with together. Interestingly very little interpretive comment was made by those involved in authorship about the new requirements in Paragraph 9. There seemed to be a general acceptance that the notion that "ethics trumps law" holds sway and that this expression of that principle was adequate.

While many in the other groups questioned the validity or meaningfulness of such an assertion, not all responses to the new requirements of Paragraph 9 were negative. Consider the following:

MR5: ... this Declaration apart from a few problems is perfectly reasonable to put in any country. And it's perfectly reasonable to say that this should be the standard. As long as it's that sort of global level it's taken at rather than ... this goes back to the things we were talking about earlier on as to which level of standard of care they're talking about. So if it's saying that it should be the best level of care in the country where you're doing the research then I don't think it's going to cause any problems. If it did say, and I don't think it does, it's the standard of care in the country that's sponsoring research then I think there are problems. So I think if you force people that were like us doing a study in Uganda to say 'you can't do a study in Uganda that you wouldn't do in the UK' I think that's wrong. Provided our reasons for doing it in Uganda and the Ugandans are comfortable with it. If the way that it's written would prevent that sort of thing, then I think that it's dangerous. But I don't think it's written at such specific level that it would do that because it's principles. That's how I would read it. ... I read it as principles which ... you know nothing couldn't reduce or eliminate but it's only when you get down to a much more tight level of detail as to which standard of care that there is a problem.

The following instructive exchange took place regarding the apparent changes to the DoH's statement of its own authority:

RC: ... So whereas it previously saw itself in a position, if you like, in subjugation to national requirements, it now sees itself in a position over and above.

EC17: I'm not sure I accept that account. It seems to me that previously they were emphasising that you know that people were still subject to their own national laws. Well so they are still. Nothing in this I think says "you're not subject to your national laws" but what it is pointing out is that national laws don't supersede ethical obligations if they're of a universal sort. And presumably they're saying that their intentions here are of the universal sort that should supersede national laws. It doesn't change the fact that you're still subject to them but morally speaking you ought to nonetheless do the right thing. So I don't think it's quite the same as saying the reverse is the situation – I don't think they're saying "you're not subject to your national laws..."

In teasing out further the commentator's view, however, it appears that it can be seen as agreeing with the assertion of ethical guidelines superseding national law. It is difficult to see from the wording of the question the suggestion that the DoH was saying "you're not subject to your national laws".

Some of the expert commentators expressed an interpretive view that could suggest that Paragraph 9 is in fact deeply flawed in its logic. In the first case, this is because it tends to be the absence of protective legislation or regulation that puts research subjects at risk:

EC8: ... You'd have to think of this as applying to despotic regimes because the laissez-faire situation where there are practically no legislation whatever is not a requirement – it's the absence of requirements so one has to think of something like Nazi Germany or the Soviet Union that wants to do ... where they want to do some kind of eugenics programmes where they do research – let me think if there's anything in China that might ... you know ... you know there's been a lot of talk about eugenic sterilisation in China and that of course has to be preceded by gather some kind of data about people with mental retardation or mental failings of some sort. I'm trying to think whether there is actually a research manoeuvre in there that's a requirement that people ... but it wouldn't be a requirement that doctors do something, it might be a requirement on human beings that they register or something or that they provide information but that's no different from something like mandatory infectious disease reporting which is done by name with contact-tracing but that's not called research. So if you require all people with mental

illness, say, or mental retardation, to register, even though we may argue against that on other grounds, it doesn't sound like it's a requirement for research. It's a requirement that might be a policy then that would then lead to sterilisation of the people, of the progenitors. So yes – there might be examples but I can't think of any which take the form of requirements.

Arguably the most devastating of interpretive blows to the construction of Paragraph 9 is provided in the following expert commentator's views:

EC13: ...it will have no effect and I think they need to understand that this is only symbolic. And the British Medical Association already published a book called "Medical Ethics Today" in which some of the subjects include things like what do doctors in circumstances where they're being forced or expected to participate in research that's unethical in their view. And the national medical associations are already very alert to this kind of problem. But I think if that's what they were trying to do, I would have phrased it very differently and I would simply have said that 'you know the international medical community is aware that some doctors may be in very difficult situations in terms of their capacity to comply with this and if they are they should refuse to participate. If they are put at risk because of that they should approach such-and-such. I mean that would be more helpful. And if that's all it was trying to do, if you take the kind of the first interpretation it just looks silly. If you take the 2nd interpretation then this doesn't really. I mean that has done nothing for a doctor who is trying in a country where it's quite clear that human rights abuses are going on all the time. It doesn't tell them anything. 'No national ethical... should be allowed to ...' well the doctor can't stop that happening. So it seems to me if what they're trying to do is to get at 'some of you guys are in real trouble – and here are a set of principles you can appeal to'. But I think doctors already know that and that's not going to help them if they're feeling pressurised or tortured or threatened into doing something that's unethical in their view.

If this view is accepted this paragraph would need to be entirely re-drafted. It does, arguably, read as though it were being addressed to parliamentary select committees drafting legislation or boards of directors of health-care institutions drafting governance procedures. Of course, some of those people may be medical practitioners. However, the DoH purports to give guidelines to doctors regarding the conduct of medical research and, as this commentators so incisively states, this does

not really give guidance to doctors *qua* doctors but to those drafting laws and regulations.

As mentioned in the section on "genre", EC16 expressed views regarding the status of Paragraph 9 suggesting that a legal viewpoint would assert that a jurisdiction's "law is the law" and that the question ends there. However, there are broader views than this, as this same commentator went on to state and that if the DoH is considered to be a statement of human rights, then it can rightly challenge laws that are not seen as adequately protecting the human rights stated in the document.

Finally, one of the expert commentators appealed to the tension between the self-regulation of the medical profession and the imposition of state controls in the interpretation of Paragraph 9:

EC15: They say it shouldn't be allowed to reduce protection ... I mean I ... you could I suppose draw an analogy with a critique of this sort of socialisation that you needed to have a sort of international medical federation produce a distillation of an ethic of a medical or ... a form of medical ethics. I mean it was a turning point within medical ethics because really until then medical ethics meant the etiquette between physicians. I think that's the other issue that's so important ...

RC: Until Nuremberg?

EC15: Until Nuremberg. But then what they're trying to say is it's the relationship between the physician and the state and yet what we want is freedom, ethics and that the profession should be self-regulating. We don't mind taking state money for medical research but we don't want state controls on our research.

This clearly has major implications and would require a separate study of the history and politics of the WMA to enable any conclusion to be made. However, it is a

fitting place to close the discussion of the interpretation, by the expert commentators, of the text of Paragraph 9.

6.3.7.1 Summary

Putting the view of *EC13* to one side for the moment, there seems little interpretive difference between the 3 groups – there is not disagreement about what the paragraph means or is intended to mean. There is a slight exception to this in that some disagree that it is a strong statement of the intent that, as one author puts it, "ethics trumps law" but largely the meaning is agreed. The great area of disagreement is around the effect or impact of such a statement. Of course, as mentioned, if the views of *EC13* are accepted, there needs to be a complete re-thinking of this paragraph.

6.3.8 Paragraph 6: Enhanced Obligation to Conduct Research

There were two key interpretive issues occurring in this part of the interviews. The most important related to the choice of the 4 criteria by which "even the best prophylactic, diagnostic or therapeutic methods" should be "continuously challenged through research" according to 4 criteria: effectiveness, efficiency, accessibility and quality. Several issues regarding this choice of terms emerged – most notably the absence of "safety" from among the criteria although the other terms did generate

some interpretive comment – most notably "accessibility". A further interpretive question arose over what was meant by "continuously".

Authors

One of the authors pointed out that the terms "efficiency", "effectiveness" and "accessibility" flowed out of the literature relating to "quality" (or "quality assurance"), adding the comment:

A7: ... accessibility, I contend, is probably going to move to the front of that list pretty soon. Because ... it's no good if you know how to do it and no-one can have it".

And continuing with a general assessment of the 4 criteria:

A7: So, they are to some degree, words of their time; recognition of where we are in this particular decade or two of health care.

Another suggested that perhaps "efficiency" was subsumed in the term "effectiveness":

A11: ... I see effectiveness as subsuming efficiency. I think we ought not to talk about efficiency. ... There are accountants for that. ... I simply see cost-effectiveness as part of effectiveness.

The same author also remarking:

A11: And then quality of course. Quality should be implicit.

Unfortunately it was not clarified at the time whether that meant "quality, being implicit, need not be mentioned" or whether it was implicitly obvious that "quality" should be in the list.

A few authors expressed a preference for the inclusion of the term "safety" in the list

of criteria

However, the most common defences of the existing 4 criteria (i.e., without explicit mention of "safety") were by appeal to other parts of the Declaration of Helsinki or that it was subsumed in one or more of the other criteria. There was not unanimity about which of the criteria encompassed safety and in many cases it required more than one.

Examples include:

A9: ... we said that the message of the whole Declaration of Helsinki is really one of safety and that it might be overkill to put that in there as well. ... We felt that the explicit call for safety was there already.

Another, supporting the choice of the 4 criteria:

A4: I mean you know all those kinds of words were used. When we looked at them and thought 'well how do they work when you put them together?' And we thought that it was pretty holistic, that it covered almost everything. I mean it doesn't actually say patient acceptability in a sense. And you know there was all sorts of words of that sort you can put in there.

The final concern that should be reflected upon in this regard is that if, indeed, "safety" is incorporated in the term "quality" that it was pointed out in the section above – the commentary on the 3 official language version – that "quality" was left out of the French translation.

One of the authors saw the entire DoH to encompass issues of safety although in conclusion came to an equivocal position and was happy for safety to be included if that provided clarity. The conversation is illuminating:

A6: Well, no, I thought safety comes in the rest of the document doesn't it?

RC: Right under ...

A6: There's ... quality ... no, I agree if clarification of safety ... but this is where the best proven and everything comes in in terms of safety.

RC: Right so the rest of the document covers it. Some have also said that quality may cover safety but that others have challenged the absence of safety. I'd also like to ask to ...

A6: That's a good point actually to make that absolutely explicit and yes I'd take that on board. The problem is that we presume some of these things ... with everything else ... I'll make a note of that fact.

RC: It wasn't so much ... it was just really to ask you whether there was a deliberate process behind that.

A6: No definitely not. I mean the best proven involves obviously the safety aspects of that. I mean I suppose that would be a given throughout the whole document because we are there to protect the patient and therefore safety is our prime concern. If you look at our basic principles, the first principle is to do good, the second principle is not to do any harm and safety comes in that.

A few minutes further into the interview, this author returned spontaneously to the issue with the following:

A6: Safety – you know you said why didn't we specifically mention it? I thought it permeated the document and if you look at Paragraph 2, that's the primary duty of the physician – "to promote and safeguard health". So – and also Paragraph 5. So I think that was a sort of given...

However, the possibility of a fairly easy-going or "laissez-faire" approach to the choice of criteria cannot be ruled out as the following conversation demonstrates:

A10: Well I forget how that came in – it was sort of ... it would be interesting to compare versions. Maybe that was there right from the beginning and people thought "that pretty well covers it". I don't recall a lot of attention being given to that ... maybe it was.

RC: The thing that comes up most often is some arguing that safety should be explicitly in there.

A10: Yeah, well it could be.

RC: Of course others have said that's part of quality.

A10: Yeah, quality. Thing like, you know, the quality movement – they were saying that quality covers absolutely everything. And quality, from that point of view, definitively includes effectiveness, efficiency and probably accessibility. But then how many people understand quality in that way.

Of course, if this (easy-going) approach were the case, then it would be hazardous – interpretation-wise – to make too much of the 4 criteria or the absence of safety. However, the danger is, of course, if an easy-going approach was taken here, then where else in the DoH? It quickly becomes evident that the interpretation of the entire document may be called into question if this conclusion is reached.

It was questioned whether "continually" was a more appropriate word in this setting. However, one of the authors defended the term continuously on the basis of the DoH being a global document:

A7: Aspirational ... the reality is when I'm sleeping you're working and when you're sleeping somebody in Japan is working ... you and I do not have to commit ourselves non-stop.

The word "continuously" was also a cause for interpretive debate. One of the authors, in particular, saw the emphasis on "continuously" as a reflection of one of

the distinctions of the medical profession from those that delivered the more technical elements of health care (without specifying what professions were envisaged):

A15: ...I guess draws out of discussion that went on throughout the 1990s about what was professionalism? ... What were the key attributes of the medical profession? ... One of the characteristics was that the doctor was the one with the "continuous spirit of inquiry" - that was the word that was used: "continuous spirit of inquiry". ... And that's the way we've got to where we are in the 20th century and it's going to be even more important in the 21st century where the contribution of an individual to a patient's whole care is as part of a team because the complexity of modern medical care means that the old days of laying on of hands is gone. We all have to play our part as part of a team and the role of the doctor in that team is to continually test the hypothesis that we're doing the right thing. So I think in my mind, that is the kind of reason why 'continuous' was in that paragraph.

Medical Researchers

Those not involved in the authorship process often found difficulty with what those drafting the DoH took to be the definitions of the 4 criteria. For example:

MR20: ... at the very least it would be interesting to know how these terms are defined. But in principle I mean the spirit of the thing is actually very good indeed.

Regarding the absence of safety, there was also on the part of some of the researchers, an interpretation that recognised "safety" as subsumed by other terms:

MR11: I think [safety] should be in quality ... this could be part of quality.

A theme that emerged in particular among medical researchers was their focus on the issue of "accessibility". In the following case, it seems simply to question the meaning:

MR1: ... The one which I do not understand completely is "accessibility". ... Um ... is it "affordability"?... I simply don't understand what it is.

While many have asserted that "quality" subsumes safety, others disagreed vociferously. Although spontaneous discussion of the criteria did not elicit much from the following, the specific question relating to quality elicited an illuminating interpretation:

RC: Now that's very interesting. A lot have raised the issue of safety not being explicitly in that list. Others have said "well quality incorporates safety as well".

MR16: I don't think it does though. I mean quality is quite precise in every industry except our own. It has been fitness for purpose. And we're saying is the research is fit for the purpose and that is to demonstrate that it's true and relevant. That's different from the excellence of the data. Or the innovativeness quality is quite precisely defined in every industry except ours.

RC: And in that you're referring to the quality of the research not the quality of the methods that are under research?

MR16: Correct.

RC: But if you are talking about the quality of ... say it's a new imaging method – part of the quality of that would be making sure that it's safe and that people aren't getting an unacceptable dose of radiation or would that not be the case?

MR16: No that would come under safety in improved imaging or cheaper or whatever ... Quality is just demonstrating that it's fit for its purpose ...

RC: So that's the image takes the picture of what you say it's taking the picture of ...

MR16: Yes.

This is one of the key counterarguments to the "quality includes safety" – the notion that quality means "fit for purpose". Further interpretive dissection of this leads to an equivocal situation. Consider an example outwith biomedical research: a bullet may

be of good quality but could it be considered "safe"? In this regard the answer depends on whether a *strong* or a *weak* interpretation of the word "safety" is used. A weak version, meaning the "bullet will only harm those it is intended to harm" (e.g., it will not blow up in the rifle and harm the shooter), could allow for the word "safety" to be subsumed. A strong definition, of course, would say that a bullet is, by definition, something intended to do harm (sports such as rifle-shooting excepted), and can never incorporate the notion of "safety". The difficulty with the above interpretation, i.e., "fit for purpose", is that it would seem to fit the "weak" definition and, in theory at least, subsume quality provided the assumption that the purpose was to "promote and safeguard the health of the patient" (Paragraph 2 of DoH). Yet the very fact that the interpretive process is so nuanced and open to confusion could be seen as an argument for explicitly including "safety"; a step that we will see was taken by the WMA in the 6th (Seoul, 2008) revision [where the term "safety" was placed first in the list of criteria].

The word "continuously" also created some interpretive confusion:

MR10: I don't know what this means.

RC: What continuous means or ... what...

MR10: The way I read it, that if it means if we have a product on the market, let's say a 5-year-old product, 10 years old, we should continue to do clinical trials which are very expensive and show that these products are equally effective to other new ... and I don't know if it means that but then it doesn't make much sense to me.

In evidence of further interpretive confusion around the absence of safety as an

explicit criterion, another researcher unequivocally states the following interpretation:

RC: Some have questioned the absence of safety as one of the criteria.

MR2: No, because it's not 'efficacy' – I think it's worded quite carefully – it's 'effectiveness' and effectiveness is the balance between safety and efficacy in real world use. So I regard effectiveness as encompassing safety.

It should be stressed that the "confusion" only emerges fully when the differing views are compared. In the above researcher's mind, the criteria were well-chosen and safety was clearly a part of effectiveness. This interviewee conveyed neither confusion in the views expressed nor equivocation about where the issue of "safety" lay. When pressed a little further:

RC: Others have said that 'quality' must incorporate safety too.

MR2: Maybe yes – I'm not quite sure what they mean by that ...

RC: It's not safety?

MR2: No, but those are my interpretations of their words and I don't know whether that was in the back of their mind or not. ... We have nothing but the words they say.

Another interesting interpretive point came after one of the medical researchers had initially commented (in a positive sense) on the broadness of scope of the 4 criteria:

RC: A couple of questions around this: you've raised the issue of the broadness of the 4 criteria – any other thoughts on the 4 criteria?

MR14: Well they imply sort of economic things don't they? Which I think often has made doctors rather nervous. Yeah, I think that doctors should accept that like everybody else, they have to operate within ... within available resources and how you allocate those resources is something that doctors need to think about even though it's rather uncomfortable.

A further comment regarding absence of the word "safety" among the research

criteria spontaneously broadens out to a difficulty with the adjective "continuously":

MR3: Well it is sort of amazing that it [safety] isn't there. It's hard to understand. Well it wouldn't be ... I'm sure everyone thinks that's important too. "Continuously challenge through research"? I'm not sure I know what that means ... you have to ask the people who wrote it.

RC: But the people interpreting and reading it also...

MR3: Yeah, we didn't perceive a requirement in there so we didn't worry about it too much.

One of the medical researchers argued that there was a deep contradiction in

Paragraph 6's expression of the requirement to "continuously challenge" even the

"best proven" methods. The dialogue is very instructive:

MR7: And as a principle, yes, we should continuously be challenging our best proven techniques. I guess I don't know if what they have in mind here is that we should constantly be striving to improve our therapies and therefore we should never accept something as best proven but always seek something better or we should actually be going back and challenging our existing practice and re-evaluating 'is it appropriate'? So there are almost two ways one could look at this. If it's best proven can we better it? Well that would not be a contradiction. If it's best proven must be re-evaluated constantly to see if it's still true then there is a contradiction.

RC: How so?

MR7: If you take that what's best proven is truly then the only you can do is try to improve it further. On the other hand, if you're challenging the evidence-base on which best proven is actually based, then one would have to go back and think about maybe placebo-controlled trials. And then there is a contradiction. So ...

RC: I see there's a contradiction within that sentence if you're saying isn't really best proven ...

MR7: Best proven doesn't mean best. It's the nature of evidence. If best proven truly is best then we can only strive to improve it rather than challenge it. But 'best proven' maybe we don't know whether it's the best. It's the best evidence we have available.

RC: That's actually a very useful insight into how that sentence works because I think you're right that it introduces a contradiction into itself if it's saying 'challenge the evidence that exists' or whether best proven is really not best proven.

MR7: If it's best proven and surely the best, then it should, it must continuously be challenged and that takes us forward. Sometimes 'best proven' in other words the treatment which is the best therapy, the efficacy can be terribly weak. There's a lot of things we do that have never been tested in randomised controlled trials. Or where I think the trials are, frankly, of very poor quality.

RC: Is it possible that that sentence can mean both?

MR7: Yes.

RC: Challenge both the evidence and the current practice.

MR7: If it does then there's contradiction. Because I've said the same elsewhere. I don't think that's the intention.

RC: Where would the contradiction be with what is said elsewhere?

MR7: Well for instance that you cannot consider placebo-controlled trials if you're proving parity. What is the quality of evidence? It comes back to hypnotics again. The quality of evidence for most hypnotics is extraordinarily poor. The nature of the study is that most of the studies were done in the 1960s or 70s. The placebo-controlled studies were done in the 60s and 70s when the standards of reporting, understanding of the natural history of the condition were very poor. Nevertheless these are now established practice in certain... When I come to do my HTA report we are taking it as read that the benzodiazepines are effective and appropriate and comparing the new drugs to the benzodiazepines when maybe the whole evidence for the benzodiazepines is based on sand. So how can you have rigorous evidence at the next stage of the review ...

RC: Very interesting ...

MR7: ... when the first one is based on nothing.

RC: So they meet the definition of the best proven because they are ... it's the best we have, even though it's not very good so you can test them against placebo?

MR7: Because the evidence-base is thin. ... The question whether you regard that as going forward ...

RC: There's a circularity there …

MR7: … or re-questioning what has gone before.

RC: There's a circularity there that I wonder if … again, I think you may have been first to point out.

MR7: This is the question of what constitutes the quality of evidence of best proven. There's evidence there but what's the quality of the evidence and how rigorous is that and do we accept the evidence-base that already exists all the time? And sometimes we don't.

This medical researcher then went on to give further examples including trials comparing drug-eluting stents with non-drug-eluting stents in the treatment of coronary artery disease, making the point that the "next stage" of the evidence-base is being built "on what is really a very thin foundation".

However the key point around this researcher's interpretation of Paragraph 6 asks the question regarding "best proven". If it really is "best proven" then all that can be "challenged" is how to improve it (unless it can be trialled head-to-head against a putative better method). What is somewhat missing from the analysis here, however, is relating this concern to the various criteria. Even if effectiveness, efficiency and quality are beyond doubt – can accessibility be improved for example? Yet there remains a significant degree of disquiet about the interpretation of the term "best proven" and this adds another layer to the many already expressed strata of concerns.

Expert Commentators

Many of the comments from Expert Commentators suggest, too, that the

interpretation of the 4 criteria is far from straightforward:

EC18: I'm not sure that accessibility ... yes, it's interesting isn't it the effectiveness and the efficiency of course the two great evils of the 3 e's of effectiveness, efficiency and equity. I don't know whether accessibility and quality is supposed to lead correctly to them or not. The ... most research ... medical research is looking for effectiveness, it's not looking at ... I suppose at quality, yes, but in the ... unless quality means something different as part of effectiveness. The accessibility one is a very different matter altogether isn't it? I mean it really is saying – is this talking about health services research, about research into whether there's a fair distribution of benefits ... of medical benefits.

Of the 4 criteria, it seems that "accessibility" is somehow being seen as set apart from the others. Is it the one criterion that taps into questions of social justice in health care provision? It is interesting to see how equivocal many seem to be in interpreting the notion of "accessibility" thus. Most seem to approach the criterion with a view not that it should not be in the list but, rather, that they are at a loss to comprehend what "accessibility" is actually driving at through its inclusion in the 4 criteria.

This is further illustrated by the following commentator's view – describing a "tension" established by the apparent obligations imposed by the 4 criteria where it may be that they cannot all be "maximised" at once in some situations but rather will inevitably be "traded-off" against one another:

EC9: Well obviously there's a tension among them. Because research for the accessibility, for example, of a therapeutic method might lead one towards the adoption of a method which is going to be more accessible although less effective. This is one of the issues that arises in resource-poor countries when they are faced with the prospect that there are, say drugs or vaccines which would not pass muster in the developed world because their side effects are too pronounced but which are

attractive to them in the developing world because of their greater cost-effectiveness and hence accessibility to the population. Or perhaps the less extensive infrastructure that would be required to deliver them. And in those circumstances you may have a tension, because of the efficacy, efficiency and effectiveness on one side, even quality, and accessibility. But I don't have another ...

A further view of the implicit presence of "safety" in the 4 criteria draws on 2 of the other criteria:

EC9: Yeah. Well I suppose that effectiveness and quality that safety is in there implicitly.

It is perhaps not beyond reason to liken the term "safety", in this debate, to a foster child shuffled between a variety of homes and, indeed, sometimes dwelling in more than one at the same time. Here we find yet another "home" for the word:

EC12: Efficiency includes safety from my point-of-view but I would have guessed people would question that. But I think safety is part of efficiency but anyway if you wanted to clarify, you wanted to add safety I'd have no problem.

Another of the commentators did not express a view on the suitability of the 4 criteria but suggested adding another: "acceptability". However, this same commentator spontaneously made a comment that is interesting given the discussion in an earlier section of the appropriateness of the terms "must" or "should" in a statement of normative ethics:

EC17: Well opinion again. But I was surprised about the term "must". I mean it seems to me that that's too strong. But potentially any, even the "best proven" are liable to be challenged is how I would put it. "Must be continuously challenged" seems to be making it too strong but I think the underlying objective is to point out that what seems to be the best at the moment may actually be less than the best, inferior to the best. And I'm surprised actually that they don't mention here, but maybe it comes under quality, the risk profile. You know the risks are potentially

minimalisable all the time you know until … you asymptotically may reach the situation of no risk or very very negligible risk.

Another commentator, on being specifically asked about the "must" vs. "should" question responded:

EC20: Yes I think that it should be 'should' if it's used at all. Yeah. Because the 'must' makes it sound mandatory. 'Should' gives you a norm. And the normative word there provides a way of measuring and … requiring ongoing measurement … recommending ongoing measurement. If suffers a little bit from obscure English. And it tells you who it's written for when it says – you've got that classic phrase 'prophylactic, diagnostic, therapeutic' which aren't exactly commonplace English but forgive those. And when you get to 'the understanding of the aetiology and pathogenesis of disease' – 'aetiology' – again, it's a technology. Why not 'causation'? Why not go for something that's already accessible? What 'causes'? And 'pathogenesis': 'development of' or something like 'implications of'. But why restrict it to disease? You know I mean sometimes it's not so much a disease, it's a condition that one's born with. I mean if somebody wants to understand left-handedness, as a left-hander I would be insulted if that were regarded as a disease. And you nod approvingly. But at the same time, too, I can see that somebody might well like to … I know there are lots of studies being that have shown that left-handed people in countries that drive on the left have fewer accidents …

As can be seen, however, the expert commentator proceeded to give further spontaneous interpretation suggesting that the use of the word "disease" was unnecessarily restrictive in defining research. Many human factors that would not be considered "disease" (left-handedness was the example used) may also be determinants of relevant health outcomes.

Another commentator, after expressing some concern that the 4 criteria could not be providing an exhaustive set of criteria then commented that effectiveness and quality encompassed safety:

RC: What about the 4 criteria by which new methods are to be evaluated?

EC1: I hadn't thought of that ... I dare say that if this is intended to be an exhaustive set of necessary and sufficient conditions it's probably defective but I need to think about it as to way ... you probably have a follow-up question ...

RC: Well the only one that comes up repeatedly is that some have said they would like to see safety in that list.

EC1: Yeah. That's a good idea. I mean it's sort of implied by some of the others ... you could argue that it was implied by effectiveness and quality.

Another of the commentators saw safety as encompassed by 3 criteria (excluding accessibility). However, it should be noted that this had not been previously considered so was a spontaneously expressed viewpoint.

RC: Some have commented on the absence of safety as one of the criteria.

EC13: Well yeah I just took safety to be included in effectiveness, efficiency and quality but it may not be.

RC: Some have raised safety spontaneously and said they wish it was in there. Others when I raise it they say 'no it's incorporated in the others'. So I just ...

EC13: I certainly would just imagine that it would be ... I mean something is not likely to be effective if not safe; certainly I don't think it would be efficient if it wasn't safe. I suppose it might. It's interesting – I hadn't thought of that.

A particular interesting comment was made in one interview regarding the entire tone of the obligation to "challenge through research" introduced in Paragraph 6.

EC13: ... But there's also a great danger in this kind of thing because it encourages a creativity or innovation which is one of the things that we should have learned from Bristol. The Bristol inquiry really is that innovative treatment or treatment to which the doctor is relatively new can be a very dangerous path to go down until they've met their learning curve or got to the top of the learning curve. If they mean by this that every doctor needs ... I mean this could be a very innocent statement or a very dangerous one. I mean it could just be a kind of comment that we shouldn't be smug and that out there there are all these good medical researchers who are going to be challenging what you think is the right practice and they'll be feeding you back

information and the results of their research. Then it's uncontroversial. If it's trying to encourage all doctors to see themselves as researchers also then it's profoundly dangerous because most of them wouldn't have a clue how to put together a proper research design. As I say it might encourage idiosyncratic practices because a particular GP for example thinks that X might be more interesting to try than Y on a particular patient. From the legal point-of-view that's very difficult for patients because it's hard enough for them to get redress when something goes wrong and so it would add to that burden. It seems ... I'm not sure that ... it's interesting that they've put it with the sentence that goes before. You know the kind of primary purpose of medical research blah... seems to me to stand alone really.

Rather than being seen as a "good", the encouragement to research was seen as fraught with peril – encouraging doctors to "have a go" with new procedures. Of course, it could be argued that this interpretation requires the opening sentence of Paragraph 6 to be taken out of context of the remainder of the document. This commentator's previously expressed suspicions regarding the motivation behind the DoH should be noted. On the one hand, in a positive sense, this therefore represents interpretive consistency. However, on the other hand, it does ignore much else that is written in the DoH about weighing of risks and benefits, the need for independent review of proposed research and the requirement to monitor outcomes for either unexpectedly higher risks or early clear-cut evidence of benefit.

On the subject of safety, one of the commentators took a view that "best proven", rather than any of the other 4 criteria, encompassed "safety". However, it is interesting to note that the expression "terriby legalistic" suggested that this commentator did not see it as a straightforward or natural interpretation that any reader would make:

EC19: You could put it[safety] in if you wanted to, but on the other hand, if you wanted to be terribly legalistic you could say that if it's the best proven therapeutic method it must be safe.

Another of the expert commentators, on being specifically asked about the absence of the criterion of "safety", showed a process of "thinking out loud" about the matter before concluding that it was not clear-cut where safety could be implicit in the other criteria.

RC: Some have questioned the absence of the word safety there.

EC16: I was just actually ... I was thinking ... I'm not just saying that I was at that point ... but then I'd say does safety come in under quality? No, quality suggests considerations of purity and I would have thought something like ... effectiveness ... safety ... it might be a good idea to put safety in. But I wonder whether safety could be subsumed under effectiveness. Could something be very effective but unsafe?

RC: Well, thalidomide was very effective at preventing morning sickness.

EC16: Yes, you're right – safety.

RC: When I say that I don't say that with the idea that that's right because the debate has gone around and some have said "oh no it's definitely contained within and they've used a variety of the other terms. And others have said that no it needs to be there overtly ..."

EC16: I would have thought for avoidance of doubt in a document of this sort you actually need to make it intelligible, clear, and say what you mean to a non-specialist and I think that arguments that safety's subsumed under one of these is probably not substantiated - safety.

The last word was said emphatically and this interesting process of thought demonstrates the difficulty with any implicit interpretation.

Another of the expert commentators, after being prompted to comment on the absence of "safety" made first a specific observation (subsumed under efficiency)

but then went on to comment about what was seen as a shift in thinking about participation in research:

EC3: ... I am going to say I thought that there has been a public switch in attitudes to research and many ethicists have not caught up with it. Somewhere in the late 80s, early 90s there was a switch from 'research is bad and there must be gross protection' to 'research is good and we need to go into studies'. And much of that was stimulated by the HIV epidemic. Huge fight to get into studies. So now the public wants into studies. They see studies as the state of the art. And so we need to re-think what we are doing with individuals. How you promote access to studies. It's a different paradigm shift.

RC: Thank you – that is very interesting. The last ...

EC3: Paradigm shift ... bad English. It's a paradigm shift.

Another commentator described a difficulty that involved differing definitions of, in particular, the terms efficiency, effectiveness (which are in Paragraph 6) and efficacy (which is not).

EC3: Well effectiveness, efficiency – the terms are still not clearly defined in the world of ... in medicine ... I had a word with [mentioned another of the expert commentators], whom you know, about this and he said ... "they were used differently" and I would have in his terminology the opposition is effectiveness, which is the functioning in the real world, and efficacy is the effect – you give a drug, it has an effect.

RC: In here it's got 'efficiency'.

EC3: Yeah, they use 'efficiency' which is ... has to do with price as well I think as far as I know this is still another issue. But the terminology is not very clear.

RC: No, I was just wondering whether that's what would have been...

EC3: I would have, of course, you could argue efficacy is clear. You have a treatment or a diagnostic thing which shows an effect ... this is pretty clear, you need not evaluate it constantly ... but it's true, effectiveness, does it work in the real

world? And efficiency – is it cost-effective? I mean, do you get out of your investment return upon investment – this is called.

6.3.8.1 Summary

This result, from theperspective of understanding the meaning of Paragraph 6 is troubling. "Effectiveness", "efficiency" and "quality" as individual criteria, as well as various combinations of them have all, in the mind of at least one interviewee, been cited as implicitly incorporating the notion of "safety". Does it mean that "safety" effectively has a place everywhere or does it give have to lead to the conclusion that it really resides nowhere? Even the criteria of "accessibility" can lay claim to incorporating "safety" because, although never mentioned on its own, one of the expert commentators (EC9) mentioned the tension between all 4 criteria; discussing particularly the need in some resource-poor settings to perhaps trade off effectiveness with accessibility. One can easily construe "safety" as an issue lurking very close to the surface in that trade-off. However, it is impossible to escape the conclusion that by being excluded from explicit mention and thereby wandering between the explicit criteria in the minds of interpreters of the DoH, that it risks being brushed aside in the debate. The WMA presumably, in the 6th (Seoul, 2008) revision agreed in some respect. "Safety" was not only added to the list of criteria but now occurs at the head of the list.

6.3.9 Re-structuring of the Declaration of Helsinki

The re-structuring of the Declaration of Helsinki and the removal of any section pertaining to "non-therapeutic" research generated little in the way of interpretive phenomena. When specifically asked whether this could be interpreted as reducing the protection for healthy volunteers participating in research, the vast majority of all interviewees defended the DoH as offering sufficient protection; however, there were exceptions.

Authors

There was little objection or dissent to the restructured logic in the DoH that saw the removal of a specific section entitled "Non-therapeutic research". One author did make a remark that itself needs further interpretation as it is not clear whether it is in support of or sceptical of the restructuring.

A3: So once you become too specific it's like when you go to a party and you start, after the event, and you start thanking people by name you're going to forget somebody. This is what's happening. And whoever is forgotten, they're not mentioned by name, and that'll mean because they're not important.

RC: Right. So ... you gave the example of saying goodbye to people at a party by name and thereby if you leave someone out, they feel excluded.

A3: Yes. And if others are covered by generality and others are covered by name, you're saying these who are named are more important people? And if that's what you intended, that's fine. But if that's not what you intend that's what you are going to get. If that's what you want, that's okay. So I'm not really sure if it says "medical care is more important than non-medical care". And that becomes a problem once you start.

Does this imply that by no longer naming "non-therapeutic research" that the implication is that protection of healthy volunteers or others involved in such research is deemed less important? It is unclear and time constraints prevented further clarification in context. However, the general point applies and it could be possible, on one reading in any case, to suggest that the restructured document places a stronger emphasis on what used to be termed "Therapeutic Research" and is now called "Medical Research Combined with Medical Care". Certainly the emphasis in the earlier analysis made many authors, where they have stressed doctors' duties to protect patients, could provide support for this suggestion.

A comment from another of the authors also tended to back up the suggested interpretation that the restructuring of the document was intended to shift the balance somewhat towards a stronger statement of protection for patients. Within the same comment, however, was a reiteration of one of the main reasons stated for the change – that the boundary between "therapeutic" and "non-therapeutic" was very difficult to define:

A2: Let's say ... diabetic patients. They collect blood samples to find, let's say, their hormones levels - thyroxine or whatever, cortisol or whatever. And that does not have anything to do with acute treatment of these patients or it's not used for their treatment at all. It's kind of basic background information ... So ... [is] this research combined with treating these patients or their disease. ... So we thought that this is the same idea ... but not with the artificial division ... that we have general principle and then ***extra*** *protection...* [emphasis mine]

Medical Researchers & Expert Commentators

None of those interviewed on the basis of their direct involvement in the medical research enterprise gave any particularly overt interpretive views regarding the restructuring of the DoH and interpretive discussion on this aspect of the 5th (Edinburgh, 2000) revision was also sparse among the expert commentators. However, one in particular gave the interesting view that nothing had really substantively changed:

EC12: I'm saying basically I don't think they really changed it. It's a … they played a game. I don't think they really changed because additional principles for medical research combined with care. These I agree they insist adding … they still have therapeutic/non-therapeutic distinction, they just made it different.

RC: And where does that appear? Therapeutic/non-therapeutic?

EC12: Well because A and B applies to everyone and C only applies in therapeutic situations.

Another of the expert commentators was supportive of the change to the structure, quoting again the fact that many variables relating to the human state – even if not specifically relating to questions of health or disease - may be suitable topics of research. In such a case the therapeutic/non-therapeutic distinction is not helpful in the views of this commentator:

EC20: … I think it's bit of a red herring to talk about therapeutic/non-therapeutic. It's going to draw some false distinctions. As I say if you wanted to establish baseline data for height and weight in a population. Is that therapeutic or non-therapeutic? Well it may be therapeutic if you are thinking of it in terms of a dietary plan for a particular group. But if you are thinking as a 'let's simply have a description'. …

Another of the commentators equivocated about the benefit (or otherwise) of the new structure. However, it was recognised that the success or otherwise of the new structure hinged around a few key interpretive questions:

EC21: ... Is the therapeutic – non-therapeutic distinction sound? In theory, yes, in practice if often becomes very difficult. When does research become therapeutic? When it offers some potential, however unlikely, of benefit to the patient? We have in some of our legislation ... particularly dealing with issues of consent got provisions that require it to be more likely than not that the research will be of benefit to the patient before it's classed as therapeutic. So I think I'm not so much attacking the division, which I don't find particularly objectionable, as questioning how we're going to define those terms. Is there a significant history of interpretation of what's therapeutic and what isn't under the Declaration of Helsinki? Has that distinction and the criteria for that distinction been revisited? It's more the criteria that I'm interested in. You can classify an enormous amount of biomedical research as therapeutic if you have a very elastic definition of potential benefit.

Finally, another of the commentators saw the previous structure of the DoH as frankly dangerous:

EC3: ... This distinction goes back to the German regulations of 1932 – pre-Nazi. And of course, the separation historically, has always been a pretext for doing anything. Because you can always state "therapeutic" and they had easier regulations for therapeutic research than for physiological research. And you can always invent some therapeutic bent you see.

...

RC: So you see that separation as dangerous?

EC3: I see it as dangerous yes. I think this[the new structure] is good.

6.3.9.1 Summary

There was broad agreement among all groups that the re-structuring of the DoH was a positive move. The blurred boundary between "Therapeutic" and "Non-

therapeutic" research was no longer a problem. A few suggested that some issues relating specifically to "Non-therapeutic" research, such as remuneration or methods of recruitment were specific to the category and warranted a special section but, by-and-large did not support a wholesale return to the previous structure.

6.4 Interpretation: Conclusions

Is the 5th (Edinburgh, 2000) revision being interpreted consistently acted to bring together various interpretations across the spectrum of those interested in medical research ethics? With respect to placebo-controls the answer has to probably be a categorical "no". Surprisingly with respect to post-trial duty of care (Paragraph 30) and benefit to communities (Paragraph 19) there is a great deal of overlap of understanding engendered by interpretation of the text of the document. The remaining difficulties centre on the nature and extent of post-trial duty of care. Major interpretive issues with respect to Paragraph 19 revolve around the meaning of the terms "reasonable likelihood of benefit" and "population. The major interpretive disparities with respect to the remaining paragraphs are: (1) the meaning of "negative" in Paragraph 27; (2) the meaning of "identifiable" in Paragraph 1; (3) the meaning of the 4 criteria (efficiency, effectiveness, accessibility and quality) in Paragraph 6 and in particular which, if any, encompass the notion of "safety". Paragraph 9 does not give rise to differences of interpretation but differences in opinion as to the effect it can possibly have. Finally, there is a broad agreement that the landscape of medical research ethics is better mapped as a result of the re-

structuring of the document - although some of the interviewees do perhaps see an additional "outcrop of rock" with respect to a need for additional specific protections for healthy volunteers that should be "mapped" by the DoH.

This concludes the discussion of the empirical results. Perhaps a better word would be "truncates". The rich material gained in the interview discussion could engender endless discussion. It is now important to turn to the question, "What happened next?"

7. WHAT HAPPENED NEXT?

CHAPTER 7: WHAT HAPPENED NEXT?

7.1 Introduction

Time moves on and the World Medical Association decided to consider a further revision of the Declaration of Helsinki. This eventually came to fruition in the 6th (Seoul, 2008) revision of the Declaration of Helsinki.

However, in deciding on the wording of this revision, the WMA sought the opinion of several outside groups including this author and the team of supervisors of this thesis. The following represents the submission made to the WMA. Additionally, the WMA sought the views of the Royal College of Physicians of Edinburgh. They also adopted the wording of this submission as their contribution to the debate.

The format of the following is as it is because the WMA specified an exact way of representing changes suggested. It is a somewhat unfortunate fact that the submission needed to be made while the above data analysis was only partially complete and this accounts for any deficiencies or discrepancies between the content of the submission and the content of Chapter 6 above.

7.2 Explanatory Comments: Invited Submission to WMA

The Working Group of the WMA (see chapter 4 for definition of "Working Group" in WMA context) invited this author and supervisors to make a submission and the

following is the text of that submission. Part C is in tabular form and follows a specific format as requested by the WMA and so is left in that particular format. It is important for the coherent thread of argument that Part C remain. The proposed 6th revision was still in a state of flux and some of the proposed changes did not come to fruition (e.g., the addition of the word "palliative" to the phrase "prophylactic, diagnostic and therapeutic methods"). There is a section discussing this and without Part C, this would not be coherent as that proposed change did not survive the revision process. Additionally, there may be some confusion over numbering of paragraphs, with some paragraph suggestions being given the designation, e.g. 24a and 24b. In all cases, it is the numbering system in Part C that determines what particular text is being discussed in that section.

[Please note that there is a part of section A.2, consisting of approximately 800 words, that was written by Professor Kenneth Boyd and this is clearly indicated. The remainder was the work of the author of this thesis].

7.3 Text as Submitted to the World Medical Association

We divide our submission into three parts. Part A contains our general observations about the proposed revision while Part B is a paragraph-by-paragraph commentary on the proposed revision of the Declaration of Helsinki. Part C is the "marked up" revisions as requested by the WMA Secretariat in its call for comments.

7.3.1 Part A. Opening Remarks and General Observations

In this section we make observations that pertain either to the entire Declaration of Helsinki (DoH) or to several paragraphs of the DoH. Following, in Part B, is a paragraph-by-paragraph commentary on the proposed changes.

A general observation that we would wish to make is that the DoH increasingly seems to sit, rather uncomfortably, between two genres of writing. Is it to be a short statement of ethical guidelines aiming to protect the human subject (we will defend the use of the term "human subjects" below)? Or is it to be a statement of best practice in research, thus giving more detail of various processes – such as the obtaining of consent or the operation of ethics committees? The reality is that the DoH appears mostly to be the former type of document but with increasing examples of the latter appearing. This has two detrimental effects. First, it makes the statements that are more detailed statements of best practice rather than broad guidelines appear to be "bolted-on" to the DoH (Paragraphs 4 and 5 are particular examples of this – see commentary below). Second, and more importantly, by adding such detailed statements yet failing to be comprehensive in its detail, the impression is created that the many issues not addressed are of lesser importance in best research practice.

We look in more detail, for example, at the wording of lengthy paragraphs such as Paragraphs 13 and 29 in Section B of this document. However, such debate may not

be necessary if it were decided to make the DoH a rather shorter statement of ethical guidelines. It has to be recognised that the ethical conduct of medical research is extraordinarily dependent on the integrity of both researchers and members of ethics committees. Rightly so, the DoH recognises in parts of its text, that not every situation can be foreseen (e.g., with respect to post-trial provision of care) and protection of research subjects is very much in the hands of the ethics committee. Perhaps there is a case to be made that the DoH should be a shorter statement of broad principles and that the WMA, or other appropriate groups, develop separate documents pertaining to such related issues as the function and responsibilities of ethical review committees.

The word count of the current proposed version of the Declaration of Helsinki (DoH) is 2159. The existing version, even including the Notes of Clarification, contained just fewer than 2000 words. While it may be argued that an increasingly long document is inevitable as biomedical research gains in complexity, there is also merit in parsimony with words where this is achievable if for no other reason than busy physicians are more likely to read the entire document the shorter it remains. We therefore, as well as commenting on the terminology in the document, have tried throughout to find ways to stem the increase in word count where that can be achieved without sacrificing clarity of meaning.

7.3.1.1 Part A.1. Interpretation of the Document

There is a strong case for either adding a sentence in Paragraph 1 or adding a preamble to the DoH along the lines of: "The Declaration of Helsinki is intended to be read as a whole and each of its constituent paragraphs should not be interpreted or applied without appropriate consideration of all other relevant parts of the Declaration". While it would be hoped that this would go without saying, it has been our finding in our research on the Declaration of Helsinki that such is often not the case and paragraphs are frequently quoted out of context.

Paragraph 32 explicitly requires all other relevant guidelines to be considered when that paragraph is applied. However, there is no reason for restricting such a requirement to Paragraph 32; it should apply to all interpretation and application of the DoH.

7.3.1.2 Part A.2. The term "human subjects"

We wish to argue for the restoration of the phrase "human subject" to the document as the best available descriptor of the people upon whom research is conducted.

To begin with, Paragraph 1's wording raises a logical objection in that *all* biomedical research somehow *involves* human beings – either as researchers or the ones being researched. We are unaware of any biomedical research undertaken solely by other species although some research involves human beings conducting research on other species. Given that the focus of the DoH is research where the species under study is the human species, the change in wording blurs rather than clarifies the aims of the document. Although the context of the document eventually renders the meaning of "human beings" evident, such imprecision at the beginning of the document would be regrettable.

Here begins the section written by Professor Kenneth Boyd:

Although the suggestion that "human subjects" should be altered to "human beings" is understandable, in the research context, "human subject" risks being a quasi-technical term, which has instrumentalising or depersonalising overtones very much at odds with the spirit of the DoH. This quasi-technical usage reflects the idea of a human (or animal) being "subjected to" research procedures [Latin: sub+jacere, "thrown under"]. Despite its etymology however, in English, "subject" is also normally used to contrast with "object", both in grammar (the subject and object of a sentence) and in the basic philosophical distinction between a conscious subject and an inert object, or between a "person" and a "thing". This distinction is of great importance for moral philosophy or ethics, since it determines moral status. In most if not all uses other than the suggested quasi-technical one, qualifying "subject" by

"human" is generally understood to entail respect for the high moral status of that human subject, as a member of the moral community or, in Kant's term, an end in himself. In terms of common rather than quasi-technical usage therefore, there is a strong argument for retaining "human subject".

Indeed, it is the avoidance of the "objectification" of people upon whom research is conducted that is the entire *raison d'être* of the DoH.

Thus it should be seen that the phrase "human subject" (i.e., the opposite of "object") bestows considerable dignity. The human being who is being studied as part of a biomedical research project is not the "object" of research but the "subject" – the very thing upon which the research is predicated, the reason the research is conducted. Seen this way, the term "research subject" ennobles the person who the investigators are researching.

It was the objectification of people in the Nazi medical experiments that led to the formulation of the Nuremberg Code, upon which the earliest version of the DoH is so heavily dependent. Further examples of objectification, such as Tuskegee, haunt the history of biomedical research. Biomedical research, by its very nature, is a process that, even when ethically conducted on consenting people, risks a degree of objectification. Individuals become part of a sample designed to achieve adequate statistical power; individual findings are grouped, averaged and statistical analysis is performed. An individual is swallowed up in the sample being studied. The protection of dignity through the recognition of the enduring *subjectivity* of those in a

research study is, we argue, central to the DoH and the phrase "human subjects", understood in this way, is a crucial part of this.

Further reasons for considering retention of the term "human subject" can be made from arguments related to the notion of "personhood". Another possible reason for wishing to alter "human subjects" to "human beings" may be concern that "subject" might not apply to someone who lacks (mental) capacity and thus might not be protected by the DoH. This concern could be well-founded if "human subject" is to be equated with a narrow definition of "person" which (as in some "personhood" theories) requires the exercise of rationality, language, self-consciousness, moral agency etc. Other theories of personhood however require only that a person is of a kind that characteristically possesses such capacities, and others again understand "person" as a relational term – a person is someone who is held to be, or becomes a person in relation to other people. In this respect, one advantage of retaining "human subject" is that it avoids having to enter into controversial philosophical debates about personhood, by using the existing and more inclusive term: a subject (human or animal) need only possess subjectivity, which need not be rational or self-conscious, and so the term "human subject" can also be applied to those humans who lack (mental) capacity.

There still remain however, possible human subjects (in the quasi-technical sense) – those in a true persistent vegetative state (PVS) for example – of whom it may be difficult to claim that they still possess subjectivity, unless something like the relational view of personhood is taken. The strongest argument for replacing "human

subjects" by "human beings" in the DoH may be that it is necessary to include protection of those in this category. If the change to "human beings" is made for this purpose however, it will have further controversial consequences. The argument, for example, that a pre-implantation human embryo is a "human being", because the embryo is a single being of the human species, is much more difficult to resist, than the argument that a pre-implantation embryo is a "human subject", a being of the human species with subjectivity – which is much less likely to be argued even on a relational view. But if a pre-implantation human embryo is a "human being" in terms of the proposed change, it will also be difficult to deny that the embryo deserves the full protection of the DoH; and this could have major implications for the continued acceptance of the DoH in countries where research on human embryos is permitted by law.

Here ends the section written by Professor Kenneth Boyd.

7.3.1.3 Part A.3. "Should" or "Must"

Although "should" is used predominantly in the DoH, the word "must" occurs on some occasions where "should" would be more appropriate (e.g., last sentence of Paragraph 22). We argue for the consistent use of the word "should" in a document of the nature of the DoH. This is, as Paragraph 1 states, "a statement of ethical principles" and, as Paragraph 9 implies it transcends legal instruments in seeking to protect people who are subjects in biomedical research.

As a statement of normative ethics, the word "should" is more appropriate than "must". "Must" implies an element of legal force that confuses rather than clarifies the status of this document. In all cases, in the absence of the ability to use force to compel adherence (as would be the case in national legislation), "must" can only ever be shorthand for "must, if they are to be in compliance with the Declaration of Helsinki, …".

7.3.1.4 Part A.4. Other Changes applying throughout the document

7.3.1.4.1 "Medical" to "Biomedical" and "Physicians" to "Researchers"

The change from "medical research" to "biomedical research" throughout the document could raise objections in that it, although the document comes from the World Medical Association, it effectively broadens the scope of the document to include the research activities of other health professionals and biomedical scientists. This is accompanied by a large number of changes of the word "physicians" to "researchers".

These changes are, in our view, likely to be met with a largely negative reaction on the part of the biomedical research community. On the one hand, it is perfectly legitimate for the WMA to come to a view about all such research and to express that

view. Whether other health professions deem these views to represent an authoritative view is a matter the other professions will undoubtedly decide for themselves. There is a very strong case to be made that the WMA has considerable moral authority (as the largest global grouping of physicians) to make statements regarding ethical guidelines for physicians involved in research. The case that the WMA can make morally authoritative statements about all biomedical research is much weaker. Consider the case of independent nurse practitioners or midwives (categories of health professionals increasingly prevalent throughout the world) teaming up with biomedical scientists to propose research into various treatment modalities in which they are involved. It is difficult to see that these groups would wish to view the DoH as authoritative when they have had little or no input into drafting the document. There is a strong case that the DoH should remain a statement essentially for physicians involved in medical research and that other organisations, perhaps CIOMS or the WHO, should convene a broader grouping of health professionals if a statement pertaining to all biomedical researchers by all types of researcher is desired.

Another possible way forward, if it is determined that the DoH should be a statement applying to all biomedical research by all types of researcher is this: Has the WMA considered any kind of pre-emptive expression – probably best written as either a preamble or covering note rather than embodied in the text of the DoH? Such an expression may make a statement along the lines: "While the WMA represents a

global grouping of medical professionals, it has sought to develop ethical guidelines that give expression to the WMA's views regarding the ethical conduct of all biomedical research, even that which is not conducted by physicians, since it is our view that the ethical principles for the protection of human subjects who agree to participate in biomedical research crosses these professional boundaries. This in no way precludes other groups of health professionals or biomedical scientists from making their own statements of ethical guidelines, and they are free to incorporate (with attribution) the words of the Declaration of Helsinki, or, if they believe the ethical principles can be expressed more effectively in other words, to so express them. Where other professional groups seeking to formulate ethical guidelines for biomedical research substantively disagree with the ethical guidelines put forward in the DoH it is hoped they would be prepared to state their case for such disagreement. In this way, the WMA can continue to review the DoH to ensure it represents an appropriate and globally applicable expression of ethical guidelines for all biomedical research involving human subjects."

Such a comment would achieve the following:

i. It would make it clear that the WMA was seeking to make a statement about all biomedical research on human subjects and not just research where physicians are the researchers (for which the previous term *medical* research would have been sufficient). Such a statement presumably reflects an underlying philosophical belief that such a universal statement is possible;

ii. It would recognise that some expressions of ethical guidelines in different words are essentially synonymous and that the WMA is not making a claim to always knowing the best way to state particular ethical principles;

iii. That, although much consideration has gone into the ethical guidelines, that the WMA is not claiming *omniscience* with respect to the ethics of biomedical research. They are prepared to review the guidelines if someone else makes a stronger case for a substantively different guideline.

It is difficult to imagine that there will be a positive reaction to the broadening of scope of the DoH to all biomedical research and to all biomedical researchers. However, the above may go some way to amelioration of the inevitable reaction to one professional grouping seeking to formulate a set of guidelines applying to ALL biomedical research on human subjects.

7.3.1.4.2 Addition of "Palliative"

This seems a reasonable addition although it has the unfortunate consequence of adding length to the document. While palliative care of course involves elements of prophylaxis, diagnosis and therapy, it could be argued that it represents an approach to care that contains many additional elements not covered adequately by the other 3 adjectives.

7.3.1.4.3 Institutional Affiliations and Conflicts of interest

Paragraphs 13 (regarding ethical committee review), Paragraph 22 (regarding consent) and Paragraph 27 (regarding publication) have a degree of repetition with respect to the issue of affiliations and conflicts of interest. Another possibility that may shorten the overall document may involve a separate paragraph relating to conflict of interest, for example:

> "Researchers should openly disclose sources of funding, institutional affiliations and other potential conflicts of interest to the independent review committee as part of the approval process, to the research subject as part of the consent process and when submitting research findings for publication."

These could then be removed from the relevant paragraphs. While sources of funding, institutional affiliations and potential conflicts of interest are all that the DoH requires on publication, this would leave Paragraphs 13 and 22 free to add additional required disclosures (e.g., incentives for participation, foreseeable benefits, risks and burdens) as appropriate for the committee review and consent processes respectively.

7.3.1.5 Part A.5. Timing of the Revision

We would like to re-iterate our comments made on our initial submission about our concerns regarding the somewhat precipitous nature of the revision. In an earlier publication (Carlson RV, Boyd KM, Webb DJ. The revision of the Declaration of

Helsinki: past, present and future. *Br J Clin Pharmacol* 2004; 57: 695-713) we pointed out the tendency toward more frequent revision. This will represent only a 4-year gap since the most recent alteration (addition of Note of Clarification to Paragraph 30). Furthermore, the debate regarding the 2000 revision lasted almost four years. If the next revision is not undertaken with great care, then the pressure for yet another revision (or more Notes of Clarification) will follow and the text of the Declaration will become increasingly unstable. Even since the most recent deadline for comments (August 2007) a major book-length work on the DoH has been published (Schmidt U, Frewer A, eds. *History and Theory of Human Experimentation: The Declaration of Helsinki and Modern Medical Ethics*. Stuttgart: Franz Steiner, 2007).

While it can undoubtedly be argued that there is never an ideal time for revision, and there are some matters that require fairly urgent attention – such as the status of the Notes of Clarification - we urge the WMA to consider postponing the 6th revision of the DoH at least until 2009 thus allowing for a 5-year gap since the last revision. This will allow the findings of the new book to be assimilated by those with an interest in commenting on the DoH. Additionally, it would allow the committee working on the proposed revision to compile a list of broad principles (such as some of the ones we raise above regarding application of the DoH to all biomedical research, the degree of detail in the document, references to legal instruments in the light of Paragraph 9 and so forth as well as many other suggestions that will

undoubtedly be forthcoming from others). It seems to us that these should be debated openly and subject to a vote at the WMA Assembly. Thus the revision would be a two-stage process but the drafting committee would have clear guidance as to the direction the document is to take with respect to these important general principles.

7.3.2 Part B. Paragraph-by-Paragraph Comments

7.3.2.1 Paragraph 1

As discussed above, there is a strong case for the retention of the term "human subjects" in the DoH. Whether or not the phrase "human subjects" is restored, we suggest the adjective "health-related" be placed before "data". Without such an addition, the DoH could be construed to be applying any human research data whatsoever. This would include, for example, market research into supermarket shopping preferences and political polls undertaking research into voting intentions. While it may be argued that just about every aspect of human behaviour could in some way eventually be linked to health, the opening paragraph of the DoH is not the place to make this point. Rather a precisely worded statement setting out the envisaged mandate of this document is preferable. Certainly, someone wanting to

undertake research into the effects of supermarket shopping preferences on health outcomes could make the specific case in their proposals for funding and for ethical review. However, it does the DoH no service to give the implication that it pertains to every type of human data gathered.

7.3.2.2 Paragraphs 2 and 3

Regarding Paragraphs 2 and 3, we suggest combining the two paragraphs into one as follows: "It is the duty of the physician to promote and safeguard the health of people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty. Such duties are articulated in more detail in codes of ethics such as the Declaration of Geneva of the World Medical Association and the International Code of Medical Ethics. These duties of a physician are in no way diminished in the context of medical research involving human subjects".

This only removes a total of 3 words from this section but would ameliorate the increase in the total number of paragraphs. It also means that, while the DoH still makes reference to these other important ethical codes, that it does not automatically become out-of-date should any of them be emended. (If "human subjects" were able to be used, a further 3-word reduction would be achieved).

The wording as currently proposed suggests that the only duty of the physician in biomedical research is to promote and safeguard the health of the people participating in the research yet, in reality, the duties of a physician go far beyond this.

7.3.2.3 Paragraph 4

We are very concerned about the addition to Paragraph 4, i.e., "Populations that have previously been underrepresented in medical … should be provided equitable access to participation in research". This seems to be contrary to the ethical positions taken in Paragraphs 7 (medical research involves risks) and 8 (some groups are particularly vulnerable). This sentence taken on its own does very little to help the groups exemplified – pregnant women and children – and seems to represent an additional risk with little added benefit.

The proposed paragraph seems to miss the point. It is not "equitable access to research" that is the end goal. Rather it is the equitable access to safe and effective prophylactic, diagnostic, therapeutic and palliative methods. The DoH would do better to reflect this.

If there is to be a real shift in the ethical position, such a statement should probably incorporate the following:

a. recognition that new methods (prophylactic, diagnostic, therapeutic and palliative) often are applied to these groups without the prerequisite research;

b. that such research, if conducted, must be specially designed to take into account the particular vulnerabilities of these groups. The word "equitable" is unclear and the way the current proposed change is worded suggests simply that pregnant women and children should not be excluded from existing trials. However, the addition of a few of each to an already large trial will add little to the benefit and much to the risk. What is needed is either: (i) trials specifically designed to test safety and efficacy of new methods in these groups or (ii) intensive monitoring if new methods (after licensing) are used in these groups. Perhaps, therefore, there should be a sentence stating that new methods should not be actively marketed outside of the groups in which research establishing safety and efficacy has taken place.

If the sentence regarding equitable access to research is retained, there should be an additional paragraph along the lines:

"It must also be recognised that newly developed prophylactic, diagnostic, therapeutic and palliative methods must either

(i) be adequately researched in groups such as pregnant women or children or other groups traditionally underrepresented in research before these methods are licensed for use in people in these groups; AND

(ii) off-license use in these groups should be subject to intensive monitoring for their safety and efficacy after they are licensed for use; AND

(iii) no positive marketing should be undertaken for use of any prophylactic, diagnostic, therapeutic and palliative methods beyond the populations in which adequate research into their efficacy and safety has been undertaken". The provisions of Paragraph 32 are of particular consequence in this regard.

7.3.2.4 Paragraph 5

We are not convinced that there is a need to add "and the sponsors of research" to this statement. Such an addition implies that the sponsors of research are somehow outside the bounds of "science and society", which is not true. There probably needs to be further consideration of the way this statement seems to imply that the interests of the individual and the interests of science and society are opposed to one another when that is often not the case. More sophisticated models of the dialectic implied in this statement need development and our research group is in the process of considering this. However, for the purposes of the current version of the DoH, we recommend that Paragraph 5 remain unchanged from earlier versions.

If it is deemed necessary to specifically include reference to the interests of the sponsors of research, then perhaps a further reference should also be made to the career ambitions of researchers. In many jurisdictions, including the United

Kingdom, career advancement and institutional funding (even from government sources) is highly dependent on "research performance"; usually assessed by measuring some combination of grants awarded, number of papers published, impact factors of the journals in which papers are published, number of citations and other markers of esteem such as invitations to speak at conferences etc. The competitive nature of modern biomedical research means that the career aspirations of ambitious individuals are as likely as the "interests of the sponsor" to compromise focus on the interest of the individual research participant.

The logical inconsistency mentioned above could be ameliorated somewhat by using the terminology: "considerations related to the well-being of the individual should take precedence over the interests of science and society, in particular the interests of the sponsors of research and the aspirations and ambitions of the researchers".

7.3.2.5 Paragraph 6

As mentioned, we agree with the addition of the word "palliative" to the adjectives describing procedures. The 2nd sentence could save on some words by reading, "Even the best proven of such procedures…" rather than a full repetition. Additionally the adverb "continually" may be preferable to "continuously" as a more realistic expectation of what is expected through this paragraph.

The term "safety" should be added to the list "efficiency, effectiveness, accessibility and quality". While there is widespread agreement that safety is something important in this context there is considerable disagreement about where, if anywhere, amongst the four terms used that safety rests. A working group of the WMA determined that safety was incorporated in the concept of quality. This is problematic in that the French version omitted the word quality from Paragraph 6 (see our publication Carlson RV, van Ginneken NH, Pettigrew LM, Davies A, Boyd KM, Webb DJ. The three official language versions of the Declaration of Helsinki: what's lost in translation? *J Med Ethics* 2007; 33: 545-548). Many have commented to us that quality could be interpreted in the sense of "quality control", e.g., of an industrial process. A factory may be producing cyanide, and the requirement for quality simply means that the cyanide produced meets adequate standards of purity of chemical composition. It would certainly not be "safe".

Others have seen quality as incorporated in "effectiveness" – seeing effectiveness as defined as a kind of "net effectiveness" – taking into account both the benefits and harms of a prophylactic, diagnostic, therapeutic or palliative method. Whatever is the case, it seems that an explicit inclusion of the term safety would add considerable clarity to this sentence.

Another concern is that, while this paragraph rightly promotes challenging even "the best proven" knowledge claims in biomedicine, that these are often not the highest

priorities for scarce research resources. There should be consideration of addition of a sentence or paragraph that incorporates the just distribution of research efforts; perhaps along the following lines: "Although all medical knowledge, even that considered best proven, should be challenged through research, resources for biomedical research are limited and the development of just procedures for prioritising research should be a matter of concern for all researchers".

7.3.2.6 Paragraph 7

We agree that there is no need to change the wording of this important paragraph (other than the change to "biomedical" – if this is retained - and the addition of the word "palliative" for consistency with the rest of the document).

7.3.2.7 Paragraph 8

Consideration should be given to changing the 2nd sentence to, "Some research populations are more vulnerable than others and need special protection". This is in fact what a literal translation of the current French version of the Declaration of Helsinki would state and appears to be the thrust of the paragraph. The statement "some research populations are vulnerable" is not strictly true in that everyone being studied in research is vulnerable to some extent so, in fact, "all research populations are vulnerable". People providing confidential information are vulnerable if

researchers do not protect their data adequately. All participants in research are likely to be less knowledgeable about the research topic than researchers and so have an element of vulnerability. While the consent and committee review procedures can ameliorate such vulnerability, they can never eliminate it completely, thus there is always some residual vulnerability. And, in fact, as the modified Paragraph 4 alludes to, some populations are vulnerable to exclusion from research. The focus of this paragraph is where there is additional vulnerability by virtue of the reasons described and the wording should reflect this.

We also suggest that consideration be given to shortening the last sentence to: "These include the educationally, economically or medically disadvantaged, those who cannot give consent for themselves or who may be subject to giving consent under duress, or where research is combined with medical care". This reduces the sentence by 5 words but does not detract from the meaning.

7.3.2.8 Paragraph 9

We have no suggestions that Paragraph 9 be changed. However, serious consideration needs to be given to whether the inclusion of Paragraph 9 has ramifications for several paragraphs later in the DoH that make reference to legal requirements. Does this paragraph effectively render such references redundant? We will address this is more detail with respect to the paragraphs concerned.

7.3.2.9 Paragraphs 10-12A

We have no particular concerns about the wording of these paragraphs. There may be merit in retaining a single paragraph regarding concern for the environment and concern for animals used for research. Since the main focus of the DoH is the well-being of the human subject, and to some extent these two concerns are ancillary (though related), there is nothing lost in combining them in one paragraph and there may be gains in reducing the overall length of the DoH.

7.3.2.10 Paragraph 13

In the light of Paragraph 9, the purpose of the statement, "this committee should be in conformity with the laws and regulations of the country in which the research is to be performed" is called into serious question. If it is to specify that the committee review must take place in the country in which the research will be conducted (as opposed perhaps to the country from which the sponsorship arises), then that should be specified. The reference to conformity to law seems to potentially be in contradiction with Paragraph 9.

One of three situations must prevail. (1) If the laws pertaining to ethical review give protection equal to or greater than the in the DoH, then the researchers would follow

the legal guidelines and would also be in compliance, by definition, with Paragraph 9; (2) if the laws pertaining to ethical review give lesser protection than the DoH (but do not prohibit the more stringent ethical review), then the onus is on the biomedical research community to establish an ethical review process that goes beyond the requirements of the law and it is that standard to which researchers should adhere. The third situation is much more difficult, although arguably less likely to occur – this is where, for some perverse reason (perhaps to try to attract profitable research that cuts corners ethically), there existed laws that forbade the protections envisaged as part of ethical review. In such a case, biomedical researchers would, to be in keeping with the intent of the DoH (certainly with regard to Paragraph 9), probably be under some obligation to seek independent ethical review of the proposed research elsewhere before conducting research in that jurisdiction. If such a committee were to give an unfavourable ethical opinion of the proposed research, the researchers could not conduct the research (even though it may be in conformity with the laws of the jurisdiction where the research is to be performed) without violating the ethical norms of the DoH. Physicians finding themselves in such a situation would be under an obligation to lobby for a change in such legislation and may, in more extreme circumstances, need to resort to civil disobedience to be true to the ethical norms of the medical profession with respect to the conduct of medical research.

Therefore the sentence regarding conformity with the laws either needs substantial modification or perhaps this requirement should go without saying and be subsumed by the requirements of Paragraph 9.

We also suggest that consideration should be given to adding, in the final sentence of Paragraph 13, "and provisions for treating and compensating participants who suffer injury as a consequence of research interventions". Such provision would require researchers to ensure (and ethics review committees to check) that adequate insurance provisions were in place, particularly for unforeseen serious consequences such as those occurring in the Northwick Park Phase I trial in London in 2006.

7.3.2.11 Paragraph 14

We are uncertain as to why the 2nd sentence – reflecting the words from the Note of Clarification to Paragraph 30 - is included in this section given that this sentence will exclusively apply to situations where research and clinical care are combined. It would not normally be expected that healthy volunteers, for example, would be in a situation at the end of a study where post-trial access was needed. If what is intended here is that those participating in a phase I trial would be identified as having access, should they go on in later life to develop a relevant health condition, then this is a very sweeping change indeed and should be more explicitly stated.

7.3.2.12 Paragraph 15

Notwithstanding our comments above regarding the widening of the scope of the DoH, we have additional concerns with the wording of this paragraph. The DoH (and, arguably, rightly so in the interests of brevity) does not further subdivide the term "researcher". The people covered by the term "researcher" vary widely. On the one hand they may be senior scientists who are not health professionals, but who are principal investigators in large well-funded projects (and who require appropriate supervision by a clinically trained individual where the research may have an impact on participants' health). On the other hand, they may be medical students or other trainees in other health-care professions undertaking small research projects as part of their training where appropriate supervision by qualified seniors is the key.

Thus, in Paragraph 15, the phrase "scientifically qualified" is obscure. If a medical student has had appropriate training in whatever procedures are required (e.g. performing venepuncture, measuring blood pressure) and is acting under the appropriate supervision of a competent and qualified physician, this would not seem to pose any ethical difficulty (assuming also that the participants were aware of the medical student's status and were not deceived into thinking they were fully qualified). However, the wording of this could be construed to mean that, since the medical student did not have a scientific qualification, he or she should not be acting in this capacity. We suggest that it is competence, based on adequate training, that is

the issue here and we would suggest a better wording would be: "Clinical research involving human subjects should be conducted only by suitably trained persons under the supervision of a competent health professional". This avoids any confusion surrounding what is meant by "qualified" (which usually means having a qualification) and, indeed, what is meant by "scientifically" while at the same time ensuring that any interventional biomedical research conducted on people, where there may be an implication for that person's health, is supervised by someone who is appropriately trained in health care.

The 2nd sentence, although it has long been present in the Declaration of Helsinki, is also somewhat unclear in what it requires and is perhaps ultimately unrealistic. It is difficult to envisage that for all research that meets appropriate ethical standards, that there is never *any* responsibility on research participants. Even the best explanation, for example, of possible side effects of a trial medication may require the active reporting by the participant of the occurrence of that side effect. Perhaps clearer wording might be: "Even after the participant has had the foreseeable risks and burdens explained and has consented to participate in research, all researchers retain the responsibility to make every effort to minimise any possibility of harm to the participant occurring as a result of the research". This would seem to encompass what is meant by this sentence in that the participant, even in agreeing to accept that there are risks and burdens foreseen in the research study, does not thereby take from

the researchers the responsibility to do their utmost to prevent the occurrence of these or any other harmful outcomes.

7.3.2.13 Paragraph 15A

The comments in relation to Paragraph 8 are pertinent here as well. To some extent *all* populations are vulnerable. We have no objection to the change in location of this Paragraph from 19 to 15A. However, we see no particular advantage in the change of wording and would advocate a return to the text that was Paragraph 19 in the 2000 revision of the Declaration of Helsinki. We suggest that the wording of the previous Paragraph 19 was an excellent expression of an important ethical principle in research. There were of course interpretation issues surrounding what constitutes a "reasonable likelihood" and how a "population" should be defined in this context. However, it was a clearly-worded important safeguard – especially against research conducted in deprived populations where the benefits would foreseeably be transferred largely to wealthier populations.

One objection to the paragraph was that it may preclude doing research in a developed country on conditions prevalent in the developing world (e.g., bilharzia infection, malaria etc.). However, the populations of the developed world have much more mobility with respect to travel than have the poorer populations of much of the developing world. Thus it would be reasonably likely to benefit the developed

population if, say, malaria were eradicated from a part of Africa, because there is a reasonable likelihood that members of that population would travel there. The converse, however, is generally much less likely.

Another objection to this paragraph has been that it raises questions about the justification of research in healthy volunteers. However, if the research is on a condition that is of importance to the population under study, the healthy volunteers have a reasonable likelihood of benefit by virtue of:

i. the possibility that they may one day develop the condition under research (there are exceptions, of course, for example male healthy volunteers should not be enrolled in a phase I trial for treatment of a condition only affecting women and vice versa);

ii. the greater possibility that loved ones or friends may have the condition under research and may obtain more immediate benefit. Generally people benefit from seeing the health of their loved ones and friends improve.

7.3.2.14 Paragraph 16

We have no particular concerns about the first 2 sentences. However, the 3rd sentence does not seem to take into account the fact that not all jurisdictions will have such a database register established. In any case, this requirement seems only to be a subset of the previous sentence and possibly could be considered an example of our

concerns expressed in the opening remarks that the DoH is dangerously caught between two genres of document: a broad statement of ethical guidelines and a detailed statement of best practice.

7.3.2.15 Paragraph 17

We've no specific suggestions about this. However our general remarks about the term "human subjects" apply here.

7.3.2.16 Paragraph 18

We agree that the 2nd sentence added nothing and the weighing of risks against the importance of the objective applies to healthy volunteers as much as to other populations. This paragraph represents an occurrence of the word "objective" and illustrates a place where this would be seen in contradistinction to the notion of the "human subject"; the research project has "objectives" and rightly so, but the people on whom the research is conducted never lose their subjectivity and should never be made objects in the fulfilment of the objectives.

7.3.2.17 Paragraph 19

This is moved to become Paragraph 15A and is commented on, in that context, above.

7.3.2.18 Paragraph 20

We have some concern about the use of the word "competent" in this and ensuing paragraphs. Increasingly, in the UK and other parts of the word, the term is being replaced by "having capacity", i.e., appropriate decision-making capacity. The relevant antonym then becomes "incapacity" rather than "incompetent"; the former considered less disparaging than the latter. So for example, we have the Adults with Incapacity (Scotland) Act 2000 governing the treatment (and enrolment in research) of people of legal majority whose relevant decision-making capacity is impaired.

The phrasing might be more awkward, e.g., this paragraph would become, "Participation by individuals with decision-making capacity in biomedical research involving human beings [sic] must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual with their own decision-making capacity may be enrolled in a research study unless he or she freely agrees to do so".

7.3.2.19 Paragraph 21

These proposed changes both shorten and improve the wording and intent of this paragraph. However, the word "personality" is somewhat unusual in this context. It presumably is important to have such a word or similar in that it incorporates notions

of keeping someone's social integrity (personality incorporating the way the research subject relates to other people) as well as their mental and physical integrity. Thus it is in keeping with a "biopsychosocial" model of health. However, we suggest that a better wording for the last part of this paragraph would be "minimise the impact of the study on their physical, mental and social integrity".

7.3.2.20 Paragraph 22

In general this paragraph, although lengthy, poses no particular problems. However, in the last 2 sentences we suggest the following changes: "After ensuring that the potential subject has understood the information, the physician should seek this person's freely-given consent, preferably evidenced in writing. If written evidence of consent cannot be obtained, the non-written consent should be formally documented and witnessed".

Written consent or a signed consent form do not, in themselves, represent *consent* (which is an ongoing relationship between researcher and subject) but rather *evidence* of consent. There is a risk that signing a consent form be seen as a form of binding contract on the research subject but such is not the case. It seems appropriate that the DoH reflect the fact that the written document represents evidence of consent rather than consent *qua* consent.

There may also be scope for shortening this paragraph if the suggestion to add a separate paragraph regarding declaration of conflicts of interest is adopted.

7.3.2.21 Paragraph 22A

This seems an important addition. With the change (in the 2000 revision) to Paragraph 1 incorporating observational research on human data into the DoH, there has been a need to recognise the differing ethical requirements between purely observational research and interventional research.

Our main concern about this proposed paragraph is the adjective "large" before databases. This seems to unnecessarily introduce the difficulty of defining what is a "large" database. The same requirement would seem to apply to "medium-sized" or "small" databases and such terms are always going to be relative in any case. With the latter there may be an increased concern about the possibility of loss of confidentiality but if this is the reason for the incorporation of the word "large", it would be preferable to make an explicit statement about the requirement to preserve confidentiality in epidemiological research rather than seemingly confine the auspices of this paragraph to "large" databases.

7.3.2.22 Paragraphs 23-26

Apart from our general observations regarding the use of the term "human subjects" and "incompetent" and the broadening of the DoH to all researchers and all biomedical research, we have only one further observation about the paragraphs pertaining to consent. Again, it stems from the incorporation of Paragraph 9. It seems that the reference to "legally authorised representative" is problematic. Ethically the proxy consent should be obtained from someone the researcher is confident will take into account the research subject's previously expressed wishes and, where these are unknown, the research subject's best interests. While the researcher should not go against the relevant local law, if the researcher is not confident that the "legally authorised representative" is in a position to either know the previously expressed wishes, or may not be acting in the subject's best interests, then despite the legality of the proxy consent, the researcher (again to be complying with Paragraph 9) should not accept such a person's consent for the subject's participation in research.

Finally, although, in general, we have no particular concerns about the wording of the paragraphs relating to consent, this is another example of where the DoH seems caught between a broad statement of ethical principles and detailed procedures (see the discussion in section A.1 above). Could there be scope for reducing them in length? From an ethical point of view, for consent to be valid it must be obtained in such a way that is free of coercion and free of deception. In many respects, what is outlined in some detail in these paragraphs could be subsumed in such a statement.

7.3.2.23 Paragraph 26A

This seems a balanced statement regarding consent for research on tissue samples. The final sentence, by using the term 'and/or', provides both protection for subjects and flexibility to undertake research where consent is not possible (e.g. where the person who provided the tissue sample is deceased).

7.3.2.24 Paragraph 26B

We think the reasons for including this paragraph require greater clarity. Is this not already potentially incorporated under provisions relating to the weighing of risks and benefits (an exclusion factor that could be required by ethics committees is that someone has not participated in other trials within a specified period of time for example) and in the provisions relating to disclosure of incentives to potential research subjects?

What are the difficulties with such "professional" participants? Is the concern primarily regarding the participant's health? (If so, the risk/benefit consideration should apply). On the other hand, is the difficulty related to the fact that repeating research on the same individuals scientifically impedes the research by reducing its generalisability to larger populations?

This paragraph seems to us to be an example of what we commented on in our opening remarks and seems to be "bolted on" rather than coherent with a general statement of ethical principles. The matter should be dealt with by ethics committees on a case-by-case basis rather than specific in a statement of general ethical guidelines.

Another alternative, if it is the vulnerability of "professional participants" rather than scientific validity that is in view here, would be to mention this in Paragraph 8 regarding vulnerable populations and this alternative is reflected in Part C (the "marked-up" changes to the DoH) of this chapter.

7.3.2.25 Paragraph 27

The "obligation to preserve accuracy" is, in our view, a better expression than "accountable for". The former statement clearly states the ethical requirement regarding honesty. In the latter there is a lack of clarity. A worst-case scenario implies that as long as researchers can "adequately account for" why they tampered with the accuracy of results, that would be acceptable. We are uncertain why the previously clear statement requires any change.

We are also uncertain as to the need for the addition of the sentence, "In so doing they should adhere to accepted guidelines for ethical reporting". It would seem that

the opening statement about ethical obligations on authors, editors and publishers would also cover anything required by this additional sentence. It seems an unnecessary lengthening of the paragraph.

We have found some misinterpretation of the sentence, "Negative as well as positive results should be published…". Some have interpreted "negative" to mean "adverse" while others interpret "negative" to mean "no difference was found between the experimental group and the control group". Our understanding is that "negative" is primarily intended to make the latter point so that publication bias does not result from the fact that researchers and publishers are more enthusiastic to publish findings that are dramatically new rather than those that confirm the status quo. We are uncertain of the best way to resolve this potential difficulty in interpretation but wished to make the group drafting the proposed revisions aware of it.

7.3.2.26 Paragraph 28

We support the proposed addition of the words "and if he or she is convinced … will not adversely affect the care of the patient".

7.3.2.27 Paragraph 29

The version as proposed is very problematic. It essentially commits the DoH to take a stand against placebo except for testing of treatments for minor conditions with a

zero tolerance of added risk of "serious or irreversible harm". This is only slightly different from the 2000 version that created the response eventually leading to addition of a note of clarification. The likely response will either be similar or the Declaration of Helsinki will be ignored (as has already been advocated by major research stakeholders such as the U.S. Food and Drug Administration). It is also somewhat incongruous from an ethical point-of-view that, as a society, we permit people to take risks of serious or irreversible harm in the interests of work or leisure pursuits but that they be completely barred from doing so in the interests of further medical knowledge. Having said this, there still needs to be solid ethical boundaries around placebo-controlled methodology for people with any condition for which proven treatment exists. If this issue is engaged with serious thought, rather than subject to a rather blanket application of the "active control orthodoxy", we argue that unethical use of placebo is less rather than more likely to occur.

What we have stated above applies in this paragraph as well: there is an extraordinary reliance placed on the integrity of the well-functioning ethical review committee in protecting research subjects. It may be that, rather than state a lengthy list of considerations related to placebo use, a reiteration of our dependence on the ethical committee is all that can really be said. They are responsible both for weighing up the potential risks against the potential benefits of research (thus asking the question: "Is it reasonable to ask *anyone* to accept the risks inherent in this research?") as well as evaluating the validity of the proposed consent procedure (thus

asking whether the subject has been fairly asked the question "are *you personally* willing to accept the risks inherent in this research?"). Beyond this, it is questionable how far the DoH should make specific requirements about particular research designs. Notwithstanding this, because of the particular nature of placebo-controlled research, we would support the retention of the phrase "extreme care must be taken in making use of a placebo controlled trial" as well as perhaps the phrase "and in general this methodology should only be used in the absence of existing proven therapy". If the DoH goes along with the wording currently proposed, it will effectively be back in the situation it was in after the 2000 revision.

Should it be deemed necessary to include more detailed guidelines regarding placebo, we suggest wording along these lines:

> "Where proven prophylactic, diagnostic, therapeutic or palliative methods exist, the use of placebo, or no treatment, may be justified, provided all of the following conditions are met in the opinion of both the researchers and the independent ethical review committee:
> - the case has been made that there are compelling scientific and methodological reasons why a placebo-controlled design is necessary and that no other research method could lead to adequate testing of the hypothesis under consideration;
> - that the research design is such that any risks of any serious or long-lasting harm to participants are both minimal and proportionate to the potential benefits of the study;
> - that as part of the study participants are monitored sufficiently closely that any evidence of possible harm occurring as a result of participating in the research is detected as early as possible, and, should this occur, that any 'blinding' of patient and the health-worker responsible for the care of the patient as to what the patient is receiving is removed, and the patient is then offered the best proven active treatment indicated for their condition with no unnecessary delay, irrespective of any effect this may have on the scientific validity of the study;

- that as well as fulfilling the already stated requirements in Paragraphs 20-25 above, that particular attention be paid to ensuring that as part of the process of gaining informed consent, that there will be no misunderstanding on the part of participants regarding the fact that if they agree to participate in the research study they may receive an inactive placebo or no treatment and that participants are aware that this is despite the existence of proven active treatment and that participants' agreement to take part will be free of any coercion or deception about these facts;
- that none of the above conditions are to be fulfilled by virtue of selecting research participants from a population where the existing proven treatment methods are generally unavailable".

7.3.2.28 Paragraph 30

We suggest in this paragraph that the following sentence be incorporated: "It should be recognised that a duty of care exists towards patients even after the study is complete and that the ethical review process should ensure that such a duty of care is appropriately recognised and incorporated into the planning of the study. At the conclusion of the study...". This more explicitly states the ethical requirements of the situation without specifying exactly upon whom the duty of care will fall. It simply means that a proposal that will abandon study participants to no appropriate care whatsoever does not meet the requirements of the DoH.

In the past, one objection to the ongoing provision of beneficial methods after a study has been completed is that "the results of a single study are not usually accepted as conclusive". However, there is an important counter-observation to this. One reason such single studies are not accepted is the risk that the population under

study has some unique characteristics that would impair the generalisability of results. However, in the paragraph concerned, we are not talking about generalising the results beyond the study population but applying them to the population that has already been studied. Although new methods of patient care require more intense monitoring than well-established methods, the above observation considerably reduces the weight of the "we don't accept the results of a single study" argument.

7.3.2.29 Paragraph 31

We agree that this paragraph should remain in the DoH as currently worded.

7.3.2.30 Paragraph 32

We agree with the addition of the requirement "after seeking expert" advice. This provides a welcome safeguard against the "maverick" physician trying unproven or new methods. As above, we question whether the term "legally authorised" is appropriate in view of Paragraph 9. The ethically important point, as mentioned above, is not the legal authorisation but the confidence that the proxy consent-giver is taking into account the patient's previously expressed wishes and/or best interests.

The final sentence: "The other relevant guidelines of this Declaration should be followed" should go without saying in this immediate context. However, in view of the propensity in interpretation to lift various portions of the DoH out of context, as

mentioned above and reiterated here, there may be a case for adding a preamble to the DoH along the lines of: "The Declaration of Helsinki is intended to be read as a whole and each of its constituent paragraphs should not be interpreted or applied without appropriate consideration of all other relevant parts of the Declaration". While it would be hoped that this would go without saying, it has been our finding in our research on the Declaration of Helsinki that such is often not the case. The requirement to take into account all other relevant guidelines is a general one and not specific to this paragraph.

7.3.3 Part C. Marked-up Revisions

In its call for comments, the WMA has requested a 'marked-up' version of suggested changes to the DoH. Our suggested revisions are shown as follows. In some cases, especially where we have been unclear as to the intent of the revised or original paragraphs, we present more than one suggestion. Additionally, where we feel there is an unnecessary addition (e.g., Paragraph 5), we make our preferred suggestion as well as our suggestion if it is finally decided that the addition will remain in the Declaration of Helsinki. Where we feel it is important to stress that there are equally acceptable alternative wordings or placements of our suggested amendments, we have included a statement in the right hand commentary column on the 'mark-up'.

While we are only too happy to present this 'marked-up' version as requested, we stress that, as with interpretation of any document that seeks to be a coherent whole (including the DoH itself), that our marked-up text is only interpreted in conjunction with the relevant statements in Part A and B. We also wish to mention that the original "Call for Comments" and the subsequent request for the marked-up version come with the statement: 'For practical purposes we would
greatly appreciate a "marked up/track changes" copy of your proposed changes to the draft consultation version. This is the only way that we can deal with the large number of responses in time for the Helsinki workshop'. This seems to reinforce our concerns, mentioned in section A.5 above, about the short time frame of the revision. While we can appreciate the immense workload involved with the revision, the importance of the task means that we wish to state again our concern that those involved in drafting the document should allow themselves adequate time for careful and thorough reflection on the proposed changes as well as the opportunity to put to the WMA Assembly the major changes in policy that are being advocated (such as applying the document to all biomedical research and all researchers rather than addressing it specifically to members of the medical profession).

Methodologically, we have, in most cases, eliminated the "mark-ups" that were already present in the revised Declaration of Helsinki so that two sets of "mark-ups" are not overlapping. If we have successfully done this in all cases, then the only bold and underlined words are those we have added to the proposed revision and the only

words to which "strikethrough" has been applied are words in the proposed revision that we recommend are removed. We have not altered the comments in the right-hand column. Where we have felt it necessary to add our own comments in the right-hand column, these are underlined and made bold.

7.3.3.1 "Marked-up" suggestions as submitted to WMA:

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for ~~Bio~~Medical Research Involving Human ~~**Beings**~~ Subjects

Adopted by the 18th WMA General Assembly
Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002
Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

PREAMBLE: (this would be where we suggest the preamble be placed rather than in the actual text of the Declaration)

A. INTRODUCTION

PREAMBLE: While the WMA represents a global grouping of medical professionals, it has sought to develop ethical guidelines that give expression to the WMA's views regarding the ethical conduct of all biomedical research, even that which is not	**We have placed the preamble here in our "mark-up" to preserve the "two column" format and allow us to make the following comments alongside.** **We recommend this preamble only if**

conducted by physicians, since it is the WMA's view that the ethical principles for the protection of human subjects who agree to participate in biomedical research cross these professional boundaries. This in no way precludes other groups of health professionals or biomedical scientists from making their own statements of ethical guidelines, and they are free to incorporate (with attribution) the words of the Declaration of Helsinki, or, if they believe the ethical principles can be expressed more effectively in other words, to so express them. Where other professional groups seeking to formulate ethical guidelines for biomedical research substantively disagree with the ethical guidelines put forward in the DoH it is hoped they would be prepared to state their case for such disagreement. In this way, the WMA can continue to review the DoH to ensure it represents an appropriate and globally applicable expression of ethical guidelines for all biomedical research involving human subjects.	**the WMA continues, through the re-wording of the DoH, to apply the DoH to all biomedical research and all researchers rather primarily addressing physicians involved in research. Please see Part A.4, above, for our discussion of this issue.**
1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in ~~bio~~medical research involving human ~~beings~~ subjects. The Declaration of Helsinki is intended to be read as a whole and each of its constituent paragraphs should not be interpreted or applied without appropriate consideration of all other relevant parts of the Declaration. **~~Bio~~Medical research involving human** subjects **~~beings~~ includes research on human material and** health-related **data.**	'Medical research involving human subjects' has been changed to 'biomedical research involving human beings' throughout the document. There seems to be no good reason to exclude unidentifiable human material or data from the scope of biomedical research. **Alternatively, the 2nd sentence regarding interpretation could be incorporated as a preamble and not included in the text of the Declaration.**
2. IT IS THE DUTY OF THE PHYSICIAN TO PROMOTE AND SAFEGUARD THE HEALTH OF PEOPLE. THE PHYSICIAN'S KNOWLEDGE AND CONSCIENCE ARE DEDICATED TO THE FULFILMENT OF THIS DUTY. THIS DUTY IS ARTICULATED IN MORE DETAIL IN THE DECLARATION OF GENEVA OF THE WORLD MEDICAL ASSOCIATION AND THE INTERNATIONAL	**Combines and replaces previous Paragraphs 2 and 3. Still has same force as current version of DoH but is:** **i. shorter in word length** **ii. means the DoH no longer becomes out-of-date if either of the other documents is changed.**

CODE OF MEDICAL ETHICS. THIS DUTY IS IN NO WAY DIMINISHED IN THE CONTEXT OF MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS.	
~~2. It is the duty of the physician to promote and safeguard the health of the people who participate in biomedical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.~~	The addition makes the physician's general duty relevant to the subject of the Declaration, i.e., research. Although in other paragraphs the term 'physician' has been changed to 'researcher', here and in Paragraph 3 the Declaration is addressing physicians in particular.
~~3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's best interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."~~	This change brings the Declaration into line with the current wording of the International Code that was amended in 2006.
4. Medical progress is based on research that ultimately must include studies involving human **subjects.** ~~beings.~~ **Such research must also seek to ensure equitable access to safe and effective prophylactic, diagnostic, therapeutic and palliative methods for populations that have previously been underrepresented in biomedical research, such as children and pregnant women.** ~~**, should be provided equitable access to participation in research.**~~	Minor grammatical changes. The added sentence incorporates the suggestions of several commentators. It fits well in this paragraph.
5. In ~~**bio**~~medical research on human **subjects,** ~~beings,~~ considerations related to the well-being of the individual should take precedence over the interests of science and society**.** ~~**and the sponsors of research**~~. **OR (Alternative wording)** **5. In medical research on human subjects, considerations related to the well-being of the individual should take precedence over the interests of science and society, including the**	The addition indicates that commercial interests should not outweigh those of the research participant.

interests of the sponsors of research and the ambitions and aspirations of the researchers.	
6. The primary purpose of ~~**bio**~~medical research involving human **subjects** ~~beings~~ is to improve prophylactic, diagnostic, therapeutic and palliative procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, therapeutic and palliative methods **should** ~~must~~ **continually** ~~continuously~~ be challenged through research for their **safety,** effectiveness, efficiency, accessibility and quality. **Although all medical knowledge, even that considered best proven, should be challenged through research, resources for medical research are limited and the development of just procedures for prioritising research should be a matter of concern for all researchers.**	'Palliative' has been added throughout the document.
7. In current medical practice and in ~~**bio**~~medical research, most prophylactic, diagnostic, therapeutic and palliative procedures involve risks and burdens.	
8. ~~**Bio**~~**M**edical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are **more** vulnerable **than others** and need special protection. These include the educationally, economically or medically disadvantaged, those who cannot give or refuse consent for themselves, those who may be subject to giving consent under duress, those for whom the research is combined with medical care **and those who have recently or frequently participated in other medical research.**	Minor grammatical changes. The deletion near the end incorporates the idea that, by its very nature, research cannot guarantee that participants will benefit from the intervention. **Consider adding the suggested words instead of Paragraph 26B.**
9. Researchers should be aware of the ethical, legal and regulatory requirements for research on human **subjects** ~~beings~~ in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should reduce or eliminate any of the protections for human **subjects** ~~beings~~ set forth in this Declaration.	"be allowed to" is unnecessary.

B. BASIC PRINCIPLES FOR ~~ALL~~ ~~BIO~~MEDICAL RESEARCH

10. It is the duty of **the physician** in ~~bio~~medical research~~ers~~ to protect the life, health, dignity, right to self-determination, privacy, and confidentiality of information of **the human subject.** ~~research participants.~~	All researchers have this duty, which includes protection of the right to self-determination and confidentiality of personal health information. 'Research subject(s)' has been changed to 'research participant(s)' throughout the document.
11. ~~Bio~~**M**edical research involving human **subjects** ~~beings~~ must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation.	Minor grammatical changes.
12. Appropriate caution must be exercised in the conduct of research **that** may affect the environment, **AND THE WELFARE OF ANIMALS USED FOR RESEARCH MUST BE RESPECTED.**	Minor grammatical change. This paragraph has been divided into two because of the different topics covered.
~~12A. The welfare of animals used for research must be respected.~~	**Both of these topics – while important – are peripheral and there is no reason to lose the succinctness involved in combining them in one paragraph (see our discussion in Part B above).**
13A. RESEARCHERS SHOULD DISCLOSE SOURCES OF FUNDING, INSTITUTIONAL AFFILIATIONS AND OTHER POTENTIAL CONFLICTS OF INTEREST TO THE INDEPENDENT ETHICAL REVIEW COMMITTEE (SEE PARAGRAPH 13) AS PART OF THE APPROVAL PROCESS, TO THE RESEARCH SUBJECT AS PART OF THE CONSENT PROCESS (PARAGRAPHS 20-25) AND WHEN SUBMITTING RESEARCH FINDINGS FOR PUBLICATION (PARAGRAPH 27).	
13. The design and performance of each research procedure involving human **subjects** ~~beings~~ should be clearly formulated in a research protocol. This protocol should be submitted for consideration, comment, guidance and approval to an ethical review committee, which must be independent of	All ethical review committees should have the authority to approve, or not approve, research proposals. Such committees should exist wherever biomedical research is conducted and therefore should not have to be specially appointed to deal with

the researcher, the sponsor and any other kind of undue influence. ~~This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is to be performed.~~ The committee has the right to monitor ongoing studies. The researcher ~~has the obligation to~~ **should** provide monitoring information to the committee, especially any serious adverse events. **As well as the requirements of Paragraph 13A, t**he researcher should ~~also~~ submit ~~to the committee , for review,~~ information regarding ~~funding, sponsors, institutional affiliations, other potential conflicts of interest and~~ incentives for subjects and provisions for treating **and compensating** participants who suffer injury as a consequence of research interventions.	specific proposals. This addition was recommended by a commentator and seems to be quite appropriate here.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate how the proposed research complies with the principles enunciated in this Declaration. ~~The protocol should identify arrangements for post-trial access by study participants to prophylactic, diagnostic, therapeutic and palliative procedures identified as beneficial in the study or access to other appropriate care.~~	The first change strengthens the obligation of the researcher to demonstrate compliance with the Declaration. The second change (additional sentence) has been transferred from the note of clarification to Paragraph 30, since it belongs more appropriately here. **This does not seem appropriate in this section as it applies to situations where research and clinical care are combined; see our comments in Part B (above).**
15. Clinical research involving human ~~beings~~ **subjects** should be conducted only by **appropriately trained** ~~scientifically qualified~~ persons ~~and~~ under the supervision of a competent health professional. **Even after the participant has had the foreseeable risks and burdens explained and has consented to participate in research, all researchers retain the responsibility to make every effort to minimise any possibility of harm to the participant occurring as a result of the research.** ~~The responsibility for the protection of human subject research participants must always rest with a medically qualified person the researcher~~	The term 'clinical research' is introduced here to distinguish the type of research described in this paragraph from other types (non-clinical epidemiological, observational, etc.) that do not require supervision by health professionals. The term 'clinically competent medical person' is unclear. In any case, other health professionals besides physicians (dentists, nurses, etc.) do conduct clinical research. Every researcher is responsible for

~~and never rest on the subject of the research participants, even though the subject has they have given consent.~~	protecting those who are involved in the research study.
15 A. ~~**MBiomedical research involving vulnerable populations as research participants**~~ **Medical research involving human subjects** is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.	This addition allows for phase one clinical trials on diseases that affect developing countries to be conducted in developed countries.
16. **All** ~~Every bio~~medical research ~~project~~ involving human ~~beings~~ **subjects** should be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them or to other individuals or communities affected by the condition under investigation. The design of all studies should be publicly available. In particular, before recruitment of the first participant, each clinical trial should be included in a database register, **or other appropriate record,** that is freely accessible by members of the public.	The first addition recognizes the importance of communities in determining the risks and benefits of a research study. The second addition is meant to exclude benefits to researchers and sponsors. The deleted sentence is unnecessary and moreover does not fit in here. The last addition was recommended by several commentators and seems quite appropriate here.
17. Researchers should abstain from engaging in research projects involving human **subjects**~~beings~~ unless they can demonstrate that the risks involved have been adequately assessed and can be satisfactorily managed. Researchers should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.	These requirements apply to all researchers, not just physicians. Researchers must demonstrate to the ethical review committee that they have taken all necessary measures to protect the research participants.
18. ~~Bio~~**M**edical research involving human ~~beings~~ **subjects** should only be conducted if the importance of the objective outweighs the inherent risks and burdens**.** ~~to the **research participants**.~~	The principle applies equally to all participants in research. Healthy volunteers are no different in this respect.
	Paragraph 19 has moved and is re-numbered as 15A.
20. Participation **in medical research,** by ~~individuals~~**human subjects with appropriate decision-making capacity,** ~~in biomedical research involving human beings must~~ **should always** be voluntary. Although it may be appropriate to consult family members or community leaders, no ~~competent~~ individual **with such capacity** ~~may~~	The first change allows for involuntary participation in research by incompetent individuals as governed by Paragraphs 24-26. The additional sentence addresses the custom in some populations whereby the

should be enrolled in a research study unless he or she freely agrees to do so.	competent individual's agreement to participate in research may need to be supplemented, but never replaced, by the agreement of another person.
21. The dignity and integrity of human **subjects** ~~participants~~ in ~~bio~~medical research must always be respected. Every precaution should be taken to respect their privacy and the confidentiality of their information and to minimize the impact of the study on their physical**,** ~~and~~ mental **and social** integrity. ~~and personality.~~	Minor grammatical changes.
22. In any clinical research involving human **subjects**~~beings~~, each potential participant ~~must~~ **should, as well as the requirements of Paragraph 13A,** be adequately informed of ~~the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher,~~ the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant details of the study. The potential participant should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential participants, as well as to the methods used to deliver the information. Potential research participants should be informed that secondary/chance findings or information on genetic disease dispositions may impact their personal or professional lives. After ensuring that the potential participant has understood the information, the researcher should then seek the potential participant's freely-given informed consent, preferably **evidenced** in writing. If the **evidence of** consent cannot be obtained in writing, **evidence of** the non-written consent must be formally documented and witnessed.	These requirements do not apply equally to non-clinical epidemiological research. Incompetent potential research participants are dealt with in Paragraphs 24-26. The term 'potential participant' is used to indicate that an individual does not become a 'participant' until consent is given. Additions suggested by the several commentators. 'Obtain' has been changed to 'seek' to emphasize the potential participant's right to either refuse or agree to take part in the research. **Logically, the researchers also "participate" in research. However, provided the meaning in context is clear, we have not always changed the word "participant" back to "subject" as it does not give rise to the same difficulties that we discuss in Part A.**
22A. In observational epidemiological research, conducted by examining ~~large~~ databases, there may	New paragraph to deal with informed consent in non-clinical epidemiological

be situations where informed consent is impossible, difficult, or unethical to obtain or poses a threat to the validity of research. Such research should be done only after consideration and approval of an ethical review committee.	research.
23. When seeking informed consent for participation in ~~the~~ research ~~project~~ the researcher should be particularly cautious if the potential participant is in a dependent relationship with the researcher or may consent under duress. In that case the informed consent should be sought by an appropriately qualified individual who is not engaged in the investigation and who is completely independent of this relationship.	These requirements apply to all researchers, not just physicians.
24. For a potential research participant **without appropriate decision-making capacity**, ~~, or is physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator~~ **the** researcher must obtain informed consent from **an ethically appropriate proxy who they are confident will take into account the participant's previously expressed wishes relevant to the situation and, where these are not known, the participant's best interests.** ~~the legally authorized representative in accordance with applicable law. These individuals~~ **Individuals without decision-making capacity** should not be included in a research study unless it is intended to promote the health of the population represented by the potential participant and this research cannot instead be performed with participants **able to give their own consent.** ~~legally competent persons.~~ Benefits and risks need to be adequately and carefully assessed in the best interest of ~~the legally incompetent~~ **those** potential research participant**s who lack decision-making capacity.**	Minor changes for clarification. The repetition of 'legally incompetent' is unnecessary. The additional sentence provides extra protection for incompetent research participants.
25. When a potential research participant without sufficient decision-making capacity, such as a minor child, is able to give assent to decisions about participation in research, the researcher ~~must~~ **should** obtain that assent in addition to the consent **indicated by Paragraph 24.**~~of the legally authorized representative.~~	

26. Clinical research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population and the research cannot be delayed. The specific reasons for involving individuals with a condition that renders them unable to give informed consent ~~must~~ **should** be stated in the research protocol for consideration and approval of the review committee. Benefits and risks need to be adequately and carefully assessed in the best interest of the potential research participants. ~~The protocol must should state that e~~**C**onsent to remain in the research should be obtained as soon as possible from the individual or ~~a legally authorized surrogate~~ **appropriate proxy**.	This does not apply to non-clinical epidemiological research. The additional requirement seems appropriate, as do the changes of 'should' to 'must'. The additional sentence provides extra protection for these research participants.
26A. In addition to obtaining appropriate informed consent for sample collection and investigation of samples, researchers should also ensure that when samples are stored for future use, consent is sought for storage. In addition, if the samples are then reused for a different purpose from that for which consent was originally obtained, appropriate consent and/or approval of the ethical review committee should be obtained for such reuse.	New paragraph.
26B. ~~Re-exposure of 'professional participant' patients to clinical trials should be actively discouraged.~~ Guidance as to the number of exposures of ~~patients~~ **research subjects** per ~~time~~ **research protocol**, or in clinical trials, should be developed by regulatory authorities, in consultation with ethics committees.	New paragraph. **This paragraph applies to "healthy volunteers" (e.g. those who frequently volunteer for phase I trials) as much as to "patients".**
27. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Researchers are **obliged to preserve** ~~accountable for~~ the accuracy of the results. They have a duty to make publicly available the results of research on human participants. ~~In so doing they should adhere to accepted guidelines for ethical reporting.~~ Negative as well as positive results should be published or otherwise made publicly available. ~~Sources of funding, institutional~~	Minor changes as suggested by commentators. Clarification and expansion of the requirement. **Requirements for declaration of conflicts of interest etc. now contained**

~~affiliations and any possible conflicts of interest should be declared in the publication.~~ Reports of research not in accordance with the principles laid down in this Declaration should not be accepted for publication.	**in separate paragraph.**

C. ADDITIONAL PRINCIPLES FOR ~~BIO~~MEDICAL RESEARCH COMBINED WI

28. The physician may combine ~~bio~~medical research with medical care~~,~~ only to the extent that the research is justified by its potential prophylactic, diagnostic, therapeutic or palliative value and if he or she is convinced that participation in the research study will not adversely affect the care of the patient. When ~~bio~~medical research is combined with medical care, additional standards apply to protect these patients ~~who are research subjects~~.	The physician's primary responsibility is the well-being of the patient rather than the advancement of science.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic**,** ~~and~~ therapeutic and palliative methods~~., except in the following circumstances:~~ **Extreme care must be taken in making use of a placebo-controlled trial and, in general, this methodology should only be used in the absence of existing proven therapy.**	The contents of the note of clarification have been incorporated in the paragraph with no changes to the requirements. In this way, the apparent contradiction between the paragraph and the note, that some commentators allege, disappears.
Placebo, or no treatment, is permitted in studies where no proven prophylactic, diagnostic, therapeutic or palliative method exists.	Unnecessary.
Where proven prophylactic, diagnostic, therapeutic or palliative methods exist, the use of placebo, or no treatment, may be justified, provided all of the following conditions are met in the opinion of both the researchers and following especially careful and detailed scrutiny by the independent ethical review committee: **- the case has been made that there are compelling scientific and methodological reasons why a placebo-controlled design is necessary and that no other research method could lead to adequate testing of the hypothesis under**	Minor change for clarification.

consideration; **- the research design is such that any risks of any serious or long-lasting harm to participants are both minimal and proportionate to the potential benefits of the study;** **- that as part of the study participants are monitored sufficiently closely that any evidence of possible harm occurring as a result of participating in the research is detected as early as possible, and, should this occur, that any 'blinding' of patient and the health-worker responsible for the care of the patient as to what the patient is receiving is removed, and the patient is then offered the best proven active treatment indicated for their condition with no unnecessary delay, irrespective of any effect this may have on the scientific validity of the study;** **- that as well as fulfilling the already stated consent requirements in Paragraphs 20-25 above, that particular attention be paid to ensuring that as part of the process of gaining informed consent, that there will be no misunderstanding on the part of participants regarding the fact that if they agree to participate in the research study they may receive an inactive placebo or no treatment and that participants are aware that this is despite the existence of proven active treatment and that participants' agreement to take part will be free of any coercion or deception about these facts;** **- that none of the above conditions are to be fulfilled by virtue of selecting research participants from a population where the existing proven treatment methods are generally unavailable.** ~~Where for compelling and scientifically sound methodological reasons its the use of placebo is necessary to determine the efficacy or safety of a prophylactic, diagnostic, and therapeutic or palliative method; or and~~ ~~- Where a prophylactic, diagnostic, and~~	Removal of apparent discrepancy between former para. 29 and note of clarification. Unnecessary.

~~therapeutic or palliative method is being investigated for a minor condition, the use of placebo is permitted if the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.~~ ~~All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.~~	
30. **It should be recognised that a duty of care continues towards patients even after the study is complete and the ethical review process should ensure that such a duty of care is appropriately recognised and that arrangements for appropriate care are incorporated into the planning of the study.** At the conclusion of the study, patients entered into the study **are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example,** access to prophylactic, diagnostic, therapeutic or palliative **methods** ~~treatments~~ identified by the study. ~~**Note of clarification on Paragraph 30 of the WMA Declaration of Helsinki**~~ ~~The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.~~	This change reinforces the ethical principle of entitlement without specifying the details of which benefits should be provided and who should provide them. **Change from "treatments" to "methods" necessary for grammatical and logical reasons: we wouldn't normally refer to "diagnostic treatments".** Moved to Paragraph 14.
31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.	
32. In the treatment of a patient, where proven prophylactic, diagnostic, therapeutic and palliative methods do not exist or have been ineffective, the	Minor grammatical changes.

physician, after seeking expert advice, with informed consent from the patient or ~~a legally authorized~~ **ethically appropriate** surrogate, may use an unproven or new prophylactic, diagnostic, therapeutic or palliative method if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this measure should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available. ~~The other relevant guidelines of this Declaration should be followed.~~	Additional protections for patients. **See Paragraph 1.**

7.4 Impact of the Submission

It is impossible to ascertain the exact impact of this submission as the "word-smithing" by the Working Group of the WMA was done "behind closed doors" on this occasion. The final text of the 6th (Seoul, 2008) revision of the DoH is reproduced in Appendix 4 so the interested reader can speculate!

On at least one occasion, the suggested wording from this submission was incorporated "word-for-word". The sentence, "The Declaration of Helsinki is intended to be read as a whole and each of its constituent paragraphs should not be interpreted or applied without appropriate consideration of all other relevant parts of the Declaration" was added almost without change to Paragraph 1 of the new revision. The minor changes were from "Declaration of Helsinki" to simply "Declaration" and from "interpreted or applied" to "applied" and "all other relevant

parts of the Declaration" to "all other relevant paragraphs". The structure of the sentence remains intact.

At the other end of the scale, it is clear that the WMA completely ignored the suggestions made regarding the former Paragraph 29 (now Paragraph 32) regarding placebo. Many of the other suggestions appear to have been taken up in one form or another but it is, of course, unknown how many other submissions made the same or similar points. As mentioned above, it will be for the reader to judge what the impact may have been, or perhaps for another researcher to delve into the archives, minutes and memories of the individuals involved in the revision process – WMA-permitting.

A further source of evidence, however, that the work in this thesis has contributed to the debate around the 6th revision and perhaps to the final text itself is found on the WMA website. Since the debate about the 6th revision began the WMA has published "Background Documents" listing a number of "useful references". Included among this list of 11 documents are the two papers emanating from Chapters 2 and 5 as well the book edited by Schmidt & Frewer, from which the work in Chapter 4 (above) contributed a chapter.

One particular disappointment was the rejection of the following suggestion in Paragraph 6: "Although all medical knowledge, even that considered best proven, should be challenged through research, resources for medical research are limited

and the development of just procedures for prioritising research should be a matter of concern for all researchers". Although the wording itself may undoubtedly be improved upon, no trace of this suggestion or anything relating to the issue of prioritisation of research appears within the DoH. This would seem a major lacuna. While it is recognised that priority may be context-specific, the complete absence of any mention of the issue seems surprising.

8. Summary and Conclusions

CHAPTER 8: SUMMARY AND CONCLUSIONS

8.1 Summary

This thesis has traced the evolution of the text of the controversial 5th (Edinburgh, 2000) revision of the Declaration of Helsinki. Through a thorough analysis of the changes to the text, those seemingly most important were selected and a semi-structured interview questionnaire constructed. The aim was to see how a series of experts draw from three groups – authors, medical researchers, expert commentators – interpreted these changes with a view to asking whether the text of the DoH was acting to being interpreted sufficiently consistently to conclude that the DoH effectively "maps" the ethical issues represented. The results are detailed in chapter 6 and show a mixed result.

Along the way, there was a detailed examination seeking to further understand the processes adopted by the WMA in modifying their ethical declarations. Additionally, the recognition that a global document would need to be interpreted across several languages necessitated consideration of how translation of the document had apparently affected it was recognised. A study showed that there were indeed differences, even among the three official versions. Some of these differences were of concern, while others helped illuminate interpretive possibilities.

Finally, as the DoH is a living document, it came forward for revision again. As a

further illumination of the possible interpretations and the areas where interpretations diverge , the detailed submission made by this author and supervisors (at the invitation of the WMA) was presented. While it is impossible to know the exact impact, some of the changes in the 6th (Seoul, 2008) revision suggest that there was some influence. This leads to the inevitable final question that will be briefly addressed in this work.

8.1.1 Has the 6th (Seoul, 2008) Revision "Fixed the Problems"?

Clearly, the answer to this is beyond the scope of this work. This work focuses on the text of the 5th revision and the controversies stirred. It would do an injustice to the methodology of this work to suggest that answering the question about divergent interpretations could be achieved with a textual analysis. It would rather require a similar exercise of speaking with those interpreting the DoH across a broad range of expertise. What might be thought to have brought together one set of interpretations may well have inadvertently opened up other areas of misunderstanding that textual analysis alone would not detect.

Having said this it is reasonable to review the findings of Chapter 6 and to ask which of the textual issues the 6th revision of the DoH addressed and how they were addressed.

8.1.1.1 "Genre" / "Intentionality" of the Declaration of Helsinki

Again, and perhaps quite understandably, no mention is made of this. The interview data above suggest that, among the authors at least, a little bit of ambiguity about the intention of the DoH was important.

8.1.1.2 Paragraph 29

1. The Note of Clarification has been incorporated into the body of the paragraph relating to placebo eliminating the confusion over the status of NoC29 relative to Paragraph 29 itself.
2. The Boolean operator connecting the two conditions where placebo may be used in presence of existing treatment has been changed from "or" to "and".
3. The phrase defining standard of control arm has changed from "best current" to "best proven current".

8.1.1.3 Paragraph 30

The effects of the old Paragraph 30 and NoC30 have been spread between two paragraphs in the 6th revision.

1. The requirement to describe plans for post-trial care at the ethics committee stage are outlined in Paragraph 14.

2. The post-trial duty of care is now defined as a requirement to provide information about the results and to "share any benefits", giving as an example "access to beneficial treatments or other appropriate care".

8.1.1.4 Paragraph 19

The requirements of the previous Paragraph 19 of "reasonable likelihood of benefit" to a community has been specifically redrawn. The requirement, now specified in Paragraph 17 of the 6th revision applies only to research in communities variously defined as "disadvantaged or vulnerable".

8.1.1.5 Paragraph 27

This is now dealt with in Paragraph 30 of the 6th revision. The lack of clarity regarding the term "negative results" in the 5th revision has been handled by adding the word "inconclusive": "Negative and inconclusive as well as positive results should be published or otherwise made publicly available".

8.1.1.6 Paragraph 1

There is a very minor change in the paragraph itself: "identifiable human material or identifiable data" is now simply "identifiable human material or data". There has however been change later in the document to reflect the broadened scope, in particular Paragraph 25 dealing in more detail with consent for use of tissue or data.

8.1.1.7 Paragraph 9

The requirements of this paragraph, that no national legal instrument should reduce the protections contained in the Declaration, have essentially been restated unchanged in the 6th revision.

8.1.1.8 Paragraph 6

"Safety" has not only been added to list of criteria by which existing methods should be evaluated but it occurs first in the list.

8.1.1.9 Structure of the Declaration of Helsinki

This remains unchanged from the 5th (Edinburgh, 2000) revision.

8.2 Conclusions

I have summarised above the findings of a detailed investigation into expert views surrounding interpretation difficulties with respect to the 5th (Edinburgh, 2000) revision of the DoH. Not unexpectedly, the DoH has been subject to a variety of different interpretations across a broad sample of experts in a variety of academic and practical fields that require interaction with ethical issues in the conduct of

medical research. Further, we have seen that the 6th (Seoul, 2008) has addressed some but not all of the textual concerns raised in this study.

What of the future of the DoH? The 6th revision has, for the first time broken the 2000-word barrier (2050 words not including the title and list of revisions). While this remains a long way off its counterpart international ethics codes such as the CIOMS document (approximately 80,000) words [CIOMS, 2002], attention to succinctness may well be an important future consideration for WMA revisions of the DoH – which still retains its brevity as a unique feature among codes of ethics addressing medical research issues.

What of the frequency of revision? The 6th revision took place 8 years after the last full revision but if the Notes of Clarification are regarded as a "form of revision" then the time elapsed was 4 years. It has been seen in the interview responses (Chapter 6) that many believe that the process of revision and the ensuing debate is just as important in sensitising the medical research world to ethical issues as the final form of the text itself. If this is the case then the gap between revisions should not be too great. However, if revisions are too frequent the text needing rapid revision may come to be seen as deeply flawed, or, at the very least, unstable.

The WMA seeks to rotate its Annual Assemblies around the 6 regions of the WMA (see Chapter 4 for details). Is there merit in putting the DoH forward for revision on

a regular basis? Perhaps a standard gap of 7 years would be suitable. This would ensure a rotation around the 6 regions. There would always be scope for "emergency" revision in the interim should it prove necessary. Equally, the WMA in the 7-year revision cycle could always decide not to change the text this time around if no change were deemed necessary. This period of time, however, would both give the text some stability but also ensure that the valuable debate is opened on a reasonably frequent basis.

In terms of further research on the DoH, a repeat of the type of study done above – interviewing a broad variety of experts – would provide an interesting comparison. Chapter 6, above, delineates the views of the text as it existed in the early years of the first decade of the 21st century. Another study considering similar questions in the early years of the 2nd decade would be a valuable means of understanding trends in how medical research ethics are best expressed in terms of a normative code around the globe. It would also be important in seeking to understand whether the DoH is waning in its influence – possibly as a result of the burgeoning number of relevant ethical codes emerging around the world; something that has been described by Ulrich Tröhler as "the wave of codification of ethics" [Tröhler, 2007].

The ethical issues surrounding the conduct of medical research will always continue to be a delicate balance between ensuring that medical research is conducted according to the highest ethical standards while at the same time avoiding unethical

"non-research". The former has been the subject of this long discussion which is now coming to an end. The latter ("non-research") issue would of course leave patients mired in a situation where they may be offered treatments based on an inadequate evidence-base. Further, it would leave those suffering conditions for which there is currently less than satisfactory treatment stuck in the *status quo*. For as long as this remains the case, well-thought-out, well-drafted documents addressing ethical issues on a global perspective will continue to be important. As long as the Declaration of Helsinki continues to meet these criteria, it should continue to send an important message to the world of medical research.

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Appendix 1: THE NUREMBERG CODE (1947)

The judgment by the war crimes tribunal at Nuremberg laid down 10 standards to which physicians must conform when carrying out experiments on human subjects.

1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent, should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment. The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs, or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results justify the performance of the experiment.

4. The experiment should be conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct and engage in the experiment.

9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of good faith, superior skill and careful judgment required of him, that a continuation of the experiment is like to result in injury, disability, or death to the experimental subject.

Appendix 2: DECLARATION OF HELSINKI 2nd (Tokyo, 1975) Revision

Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan October 1975
Recommendations guiding medical doctors in biomedical research involving human subjects

Introduction
It is the mission of the medical doctor to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the doctor with the words: 'The health of my patient will be my first consideration,' and the International Code of Medical Ethics declares that, 'Any act or advice which could weaken physical or mental resistance of a human being may be used only in his interest.'

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies *a fortiori* to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects. In the field of biomedical research a fundamental distinction must be recognised between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research the essential object of which is purely scientific and without direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research purposes must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every doctor in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Doctors are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic Principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific tradition.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interest of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Doctors should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Doctors should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the doctor is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The doctor should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the doctor should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case informed consent should be obtained

by a doctor who is not engaged in the investigation and who is completely independent of this official relationship.

11. In cases of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with the national legislation.

12. The research protocol should always contain a statement of ethical consideration involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical Research Combined with Professional Care (Clinical Research)

1. In the treatment of the sick person, the doctor must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers the hope of saving life, re-establishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method.

4. The refusal of the patient to participate in a study must never interfere with the doctor-patient relationship.

5. If the doctor considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee.

6. The doctor can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-therapeutic Biomedical Research Involving Human Subjects (Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the doctor to remain the protector of the life and health of that person on whom biomedical research is carried out.

2. The subjects should be volunteers – either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

Appendix 3: DECLARATION OF HELSINKI 5th (Edinburgh, 2000) Revision

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September, 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. Introduction

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take preference over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic,

and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this document.

B. Basic Principles for all Medical Research

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide

monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefits from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent form the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

To further clarify the WMA position on the use of placebo controlled trials, the WMA Council issued, during October 2001, a note of clarification on article 29.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

NOTE OF CLARIFICATION ON PARAGRAPH 29 of the WMA DECLARATION OF HELSINKI

The WMA is concerned that Paragraph 29 of the revised Declaration of Helsinki (October 2000) has led to diverse interpretations and possible confusion. It hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the

absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:
- Where for compelling and scientifically sound methodological reasons it is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

Note of clarification on Paragraph 30 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

Appendix 4: DECLARATION OF HELSINKI 6th (Seoul, 2008) Revision

WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on Paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.
   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison

with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

22.10.2008

Appendix 5: LIST OF INTERVIEWEES

The following participated as interviewees in the semi-structured interview process described in Chapter 6. The author wishes to take this opportunity to further thank each of them for their participation.

Dr Enrique Accorsi (Former president of WMA); Dr James Appleyard (British Medical Association); Dr Mac Armstrong (British Medical Association); Dr Richard Ashcroft (Imperial College Medical School, London); Dr Solomon Benatar (University of Cape Town); Dr Peter Boegheim (Pharmaceutical industry research and development (R&D), The Netherlands); Professor Alastair Campbell (University of Singapore); Dr Alexander Capron (World Health Organisation); Sir David Carter (British Medical Association); Sir Ian Chalmers (James Lind Library & Cochrane Collaboration, UK); Professor Francis Crawley (European Forum for Good Clinical Practice, Belgium); Professor Janet Derbyshire (Medical Research Council, UK); Professor Michel Detilleux (French Medical Association); Dr Nancy Dickey (Texas A&M University; one of the "Three Wise Women" – see chapter 4); Professor Elmar Doppelfeld (German Medical Association); Professor Len Doyal (Queen Mary University of London); Dr Mike Emanuel (Pharmaceutical industry R&D, UK); Dr Imogen Evans (Medical Research Council, UK); Mr Tom Gallagher (Pharmaceutical industry – external relations, UK); Professor Ranaan Gillon (Imperial College Medical School, London); Dr Glenys Godlivitch (Office of Biomedical Ethics, University of Calgary); Professor John Harris (University of Manchester); Dr Delon Human (Secretary-General, WMA); Dr Juhanna Idanpaan-Heikkila (CIOMS); Dr Avner Ingerman (Pharmaceutical industry R&D, Ireland); Dr Judith Kazimirski (Dalhousie University, Canada; one of the "Three Wise Women" – see chapter 4); Dr Peter Kosminski (Pharmaceutical industry R&D, Russia & Ukraine); Dr Kgosi Letlape (South African Medical Association); Dr Robert Levine (Yale University & CIOMS); Professor Chris Levy (Office of Medical Bioethics, University of Calgary); Sir Alexander Macara (British Medical Association); Professor Tom MacDonald (University of Dundee); Dr Ruth Macklin (Albert Einstein University, New York & CIOMS); Professor Sheila MacLean (University of Glasgow); Professor Ken Mason (University of Edinburgh); Professor Alexander McCall-Smith (University of Edinburgh); Dr Ian Mitchell (Office of Medical Bioethics, University of Calgary); Dr Kati Myllimäki (President of WMA & One of the "Three Wise Women" – see chapter 4; Professor Vivienne Nathanson (British Medical Association); Dr Richard Nicholson (Bulletin of Medical Ethics, UK); Professor Walter Nimmo (Pharmaceutical industry – CEO, UK); Dr Wolfgang Pfeffer (Pharmaceutical industry – R&D, Germany & Austria); vDr Tapani Piepponen (Pharmaceutical industry R&D, Finland); Sir Michael Rawlins (National Institute for Clinical Excellence, UK); Professor Povl Riis (One of 3 authors of 2nd (Tokyo, 1975) revision

of DoH, Copenhagen); Drs Bernard Schwetz & Melodie Lin – jointly interviewed (National Institutes of Health, Washington D.C.); Dr Richard Smith (British Medical Journal); Professor Anne Sommerville (British Medical Association); Dr Robert Temple (Food & Drug Administration, USA); Dr Mark Travers (Pharmaceutical industry R&D, USA); Professor Ulrich Tröhler (University of Berne, Switzerland); Professor Tom Walley (University of Liverpool); Adv Leah Wapner (Israeli Medical Association); Professor Paul Weindling (Oxford-Brookes University, UK); Dr Jarek Wiecklowski (Pharmaceutical industry R&D, Poland, Romania, Bulgaria, Lithuania, Latvia); Dr John Williams (Director of Ethics, WMA); Dr Barbara Zweiten-Boot (European Medicines Evaluation Agency [EMEA], The Netherlands).

Appendix 6: FULL ANALYSIS OF THREE LANGUAGE COMPARISON

The following details the full analysis (paragraph-by-paragraph) of the three language versions of the Declaration of Helsinki. It incorporates the three "back-translations" for each of the French-English and Spanish-English comparisons (described in chapter 5).

Three Language Comparison

Paragraph 1

English (2000 version): The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

(1996 version – Paragraph 8a from Introduction) Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects.

French (2000 version): La Déclaration d'Helsinki, élaborée par l'Association médicale mondiale, constitue une declaration de principes éthiques don't l'objectif est de fournir des recommendations aux médecins et autres participants à la recherché médicale sur des êtres humains. Celle-ci comprend également les etudes réalisées sur des données à caractère personnel ou des échantillons biologiques non anonymes.

(1996 version): Comme il s'est avéré indispensable pour le progress de la science et pour le bien de l'humanité souffrante d'appliquer les resultants des experiences de laboratories à l'homme, l'Association Médicale Mondiale a rédigé les recommendations qui suivent en vue de server de guide à tout médicin procédant à des recherches biomédicales.

Identified differences:
(1.1F) The use of the phrase 'non anonymes' in French as opposed to the term 'identifiable' in English.

(1.2F) The phrase échantillons biologiques in French is used where human material is used in English.

Back translations from French:

(1) The Declaration of Helsinki, elaborated by the World Medical Association, consists of a declaration of ethical principles, the object of which being to provide recommendations to physicians and others involved in medical research on human beings. It also includes the studies carried out on data which bears a personal character and known biological samples.

(2) The Helsinki Declaration, elaborated by the World Medical Association, constitutes a declaration of ethical principles whose object is to provide recommendations to doctors and other participants in medical research on human beings. This also includes studies made on data of personal type or non-anonymous biological samples.

(3) The Helsinki Declaration, developed by the World Medical Association, constitutes a declaration of ethical principles whose objective is to provide recommendations to physicians and other participants in medical research carried out on human subjects. This also includes medical research carried out on data of human character or non-anonymous biological samples.

1.1F: This difference persists in all 3 of the back translations. The importance of the difference hinges on whether there is a difference in meaning between identifiable and non-anonymous.

There are generally 3 levels of accessibility to the identity of people who have provided 'material' or 'samples' which are used in research. These are: (1) the identity of the research subject is known to the researcher(s); (2) the identity of the research subject is hidden by the use of a code. The code linking the identity of the subject with the sample is held by a 3rd party. The code will be broken re-linking subject with sample under strictly controlled circumstances where it is sufficiently important that the subject become aware of the results applying to his/her sample; (3) all links between subject and sample are irrevocably destroyed.

Category (1) is clearly 'identifiable' and 'non-anonymous' and category (3) is clearly not identifiable and anonymised. The question for the comparison of the English and the French versions is the status of category (2). It could be argued that the samples remain 'identifiable' because of the possibility of re-linking them with the person even though in the ordinary course of events the identity of the person will remain unknown to the researcher. In this respect they are 'non-anonymous'. Therefore it is possible that the remit of the French version of the Declaration of Helsinki would not cover category (2) with respect to the Declaration of Helsinki while the English would.

We conclude therefore that the two versions are not as identical as they could be given that the English could easily read 'non-anonymous' or the French adjective could be 'identifiable'.

1.2F This difference persists in all 3 back translations. The use of 'échantillons biologiques' in the French version is different from the English word 'human material'. A biological sample is a much broader concept and could presumably include animal or plant material. Arguably the specification of 'recherché médicale sur des êtres humains' in the previous sentence covers this ambiguity.

Spanish (2000): La Asociación Médica Mundial ha promulgado la Declaración de Helsinki como una propuesta de principios éticos que sirvan para orientar a los medicos y a otras personas que realizan investigaciôn médica en seres humanos. La investigación médica en seres humanos incluye la investigación del material humano o de información del material humano o de información identificables.

(1996 version): Puesto que es esencial que los resultados de experimentos de laboratorio sean aplicados a seres humanos, a fin de ampliar el conocimiento cientifico y así aliviar el sufimiento de la humanidad, la Asociación Médica Mundial ha redactado las siguientes recomendaciones para que sirvan de orientación a cada médico dedicado a la investigación biomedical en seres humanos.

Differences detected:

1.1S The use of the word 'propuesta' in Spanish in place of 'statement' in English.

1.2S In English 'to provide guidance' is rendered 'orient' in Spanish.

1.3S 'Seres humanos' in Spanish translates more closely as human beings or just humans (or people). The English version uses human subjects.

1.4S In English, to be explicit, the adjective 'identifiable' must be repeated for both 'data' and 'human material'. In Spanish, by using the plural form of the adjective repetition may not be necessary. The repetition of the adjective would add emphasis. Therefore it could be argued that the notion of 'identifiable' is stronger in the English than in the Spanish.

Back translations from Spanish:

(1) The World Medical Association sets out the Helsinki Declaration as a proposal of ethical principles for the guidance of doctors and people involved

in medical research into human beings. Medical research into human beings includes the research of either human material or identifiable information.

(2) The World Medical Association has proclaimed the Declaration of Helsinki as a proposal of ethical principles that serve to guide doctors and other persons who carry out medical research on human beings. Medical research on human beings includes research on human material or identifiable information.

(3) The World Medical Association has publicised the Declaration of Helsinki as a proposal of ethical principles that will guide doctors and other people who do human medical research. Human medical research includes research on identified human material or identified information.

1.1S The change from 'propuesta' in Spanish (closer to the word 'proposal' in English) persists in all 3 back translations. However, it is minor and really doesn't change the meaning. It appears to be a stylistic choice to avoid the use of the alternative 'declaración' (which translates more closely to the English 'statement') which would then occur twice in the sentence.

1.2S This perceived difference disappeared in all 3 of the back translations; the word 'orientar' being rendered 'guidance' by all 3.

1.3S The rendering of 'seres humanos' as 'human beings' or just 'humans' rather than the English version 'human subjects' persists in all 3 back translations but is a stylistic choice and really doesn't affect the meaning of this paragraph.

1.4S One of the back translations has chosen to repeat 'identifiable' for both of the nouns which it modifies. Interestingly, despite the use of the plural form of the adjective in Spanish, 2 of the back translations have only applied it to the noun which occurs nearest to it in the sentence. Therefore this strengthens the argument that the 2 versions would be closer to one another if 'identificables' was repeated in the Spanish version.

Paragraph 2

English (2000) version: It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

1996 equivalent: It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission. (para 1)

French (2000) version: La mission du médecin est de promouvoir et de préserver la santé de l'être humain. Il exerce ce devoir dans la plenitude de son savoir et de sa conscience.

(1996 version – Paragraph 1 from Introduction): La mission du médecin est de veiller à la santé de l'être humain. Il (elle) exerce cette mission dans la plénitude de son savoir et de sa conscience.

Differences detected:

2.1F In the 2nd sentence, the French version uses the masculine pronoun 'il' instead of repeating the noun whereas the English version repeats the noun 'physician'. It is interesting that this has been changed from 'Il (elle)' in the 1996 version. This reflects the 'his or her' rendering in the English rather than follow the convention of matching gender of pronoun with noun (the masculine noun médecin). In the 2000 French version, the convention is followed.

Back translations from French:

(1) The mission of the physician is to promote and preserve human health. He/she exercises this duty in the fullness of his/her knowledge and his/her consciousness [sic].

(2) The duty of the doctor is to promote and preserve the health of the human being. He exercises this duty in the completeness of his knowledge and conscience.

(3) The mission of the physician is to promote and safeguard the health of the people. He or she exercises this right to the best of his or her knowledge and conscience.

2.1F None of the back translations repeats the noun. Two of the three use gender neutral forms whereas one sticks with the masculine form in English. An involved discussion of the differences in the way that French and English deal with the notion of gender within language is beyond the scope of this work. The essential point is that with respect to research ethics, the meaning is the same.

Spanish (2000) version: El deber del medico es promover y velar por la salud de las personas. Los conocimientos y la conciencia del medico han de subordinarse al cumplimiento de ese deber.

(1996 version): La misión del medico es velar por la salud de la humanidad. Sus conocimientos y su conciencia deben dedicarse a la realización de esta misión.

No differences were detected on initial analysis.

Back translations from the Spanish:

(1) The duty of any doctor is to promote and safeguard people's health. Both doctor's knowledge and conscience must be subordinated to that duty.

(2) The duty of the doctor is to promote and look after the health of people. The knowledge and the conscience of the doctor must be subordinate to the fulfilment of this duty.

(3) Doctors must promote and safeguard people's health. Doctors' knowledge and conscience must be subordinated to that duty.

Nothing emerges from the back translations to suggest that importance differences between the English and the Spanish have been missed.

Paragraph 3

English version (2000): . The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration", and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient".

1996 version: The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration", and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient". (Paragraph 2 of the Introduction)

French version (2000): Le Serment de Genève d l'Association médicale mondiale lie le médicin dans les termes suivants: "La santé de mon patient sera mon premier souci" et le Code international d'éthique médicale énonce que "le médecin devra agir

uniquement dans l'intérêt de son patient lorsqu'il lui procure des soins qui peuvent avoir pour conséquence un affaiblissement de sa condition physique ou mentale".

1996 version: Le serment de Genève oblige le médecin dans les termes suivants: "La santé de mon patient sera mon premier souci" et le Code international d'Ethique Médicale stipule que le médecin devra agir uniquement dans l'intérêt de son patient lorsqu'il lui procure des soins qui peuvent avoir pour conséquence un affaiblissement de sa condition physique ou mentale.

Differences detected on initial analysis:

3.1F The English version describes the Geneva document as a 'declaration' whereas the French uses the word 'Serment'. Clearly the word 'déclaration' is available as that is the term used for the French title 'Déclaration d'Helsinki'. The word 'serment' translates into English as 'vow' or 'oath'.

Back translations:

(1) The Oath of Geneva of the World Medical Association binds the physician in the following words: "My patient's health will be my prime concern" and the International Code of medical ethics states that "the physician will have to act only in the interest of his/her patient when he/she provides medical attention which can result in a weakening of the patient's physical or mental condition".

(2) The Geneva Oath of the World Medical Association binds the doctor in the following terms: "The health of my patient will be my first concern" and the International Code of medical ethics says that "the doctor will act only in the interest of his patient when administering medical treatment which may cause a weakening of his physical or mental condition".

(3) The Geneva International Ethical Code of the World Medical Association bind the physician with the words, "The health of my patient will be my first priority", and the International Code of Medical Ethics declares that, "the physician must act only in the interest of the patient when providing medical care which may have the effect of weakening the physical and mental condition of the patient".

3.1F The back translations in 2 instances translate the word 'serment' as 'oath' and in one case as 'international ethical code'. This seems to confirm the difference in word. However, since this is simply the title of another document, while it may have implications for the consistency of understanding of the nature of the Geneva

document across French and English, it has no implications for the meaning of the Declaration of Helsinki.

Spanish version (2000): La Declaración de Ginebra de la Asociación Médica Mundial vincula al medico con la fórmula "velar solícitamente y ante todo por la salud de mi paciente", y el Código Internacional de Éthica Médica afirma que: "El médico debe actuar solamente en el interés del paciente al proporcionar atención médica que pueda tener el efecto de debilitar la condición mental y fisica del paciente".

1996 version: La Declaración de Ginebra de la Asociación Médica Mundial señala el deber del médico con las palabras "velar solícitamente y ante todo por la salud de mi paciente", y el Código Internacional de Ethica Médica se establece que: "el médico debe actuar solamente en el interés del paciente al proporcionar atención médica que pueda tener el efecto de debilitar la condición mental y fisica del paciente".

Differences detected on initial analysis:

3.1S The Spanish version says that the International Code "affirms" what it says while in the English this Code "declares". While there may be subtle shades of differing meaning between these two, they are essentially synonymous.

Back translations:

(1) The Geneva Declaration of the World Medical Association links the doctor with the principle: "to safeguard solicitously first and foremost my patient's health", and the International Code of Ethics states that: "The doctor must act solely in the interest of the patient when offering medical care that may have a weakening effect on the patient's mental and physical condition".

(2) The Declaration of Geneva of the World Medical Association links the doctor with the formula "to protect respectfully and above all for the health of my patient" and the International Code of Medical Ethics states that: "The doctor must act only in the interests of the patients to provide medical attention that can have the effect of weakening the mental and physical condition of the patient".

(3) The Declaration of Geneva of the World Medical Association links doctors with the formula "watch carefully and first of all my patient's health". The International Code of Medical Ethics says, "Doctors must act only for the patient's interest when medical attention is given that could reduce mental and physic [sic] patient condition".

3.1S Interestingly the back translators render "afirma que" as "states" (2 translations) and "says" (1 translation). These are rather blander than the more literal "affirms" or the English "declares". This back ups ("affirms"!) the contention that any shade of meaning difference between the Spanish and the English official versions is unimportant in this particular instance.

Paragraph 4

English version (2000): Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

1996 version: Paragraph 4 of the 2000 version is identical with the 5th Paragraph of the Introduction to the 1996 version.

French version (2000): Les progress de la medicine sont fondés sur des recherches qui, in fine, peuvent imposer de recourir à l'expérimentation humaine.

1996 version: Le progress de la medécine est fondé sur la recherché qui, en definitive, doit s'appuyer sur l'experimentation portent sur l'homme.

Differences on initial analysis:

4.1F A more literal translation of the requirement in the French version into English would be "Medical progress is founded upon research which, ultimately, can impose recourse to human experimentation". This is quite different in meaning from the English. An interpretation of the English leads to the conclusion that it is inevitable that at least some of the research evidence on which medical progress is based will involve research on human subjects. The French version makes allowance for this possibility but also leaves open the possibility that such progress will not require research on humans.

Back translations:

(1) Medical progress is based on research which, ultimately, can impose the use of human experimentation.

(2) Advances in medicine are based on research that ultimately may require resorting to human experimentation.

(3) Medical progress is founded on research which ultimately may have to resort to experimentation involving human subjects.

Therefore, this perceived difference is maintained in all 3 of the back translations and it must be concluded that the two versions say something quite different.

Spanish version (2000): El progreso de la medicina se basa en la investigación, la cual, en ultimo término, tiene que recurrir muchas veces a la experimentación en seres humanos.

1996 version: El progreso de la medicina se basa sobre la investigación, la que en ultimo término debe cimentarse en parte en la experimentación en seres humanos.

Differences on initial analysis:
4.1S The Spanish version translates more literally into "many times has to have recourse in part to experimentation on human beings". This meaning would seem to somehow be intermediate between the French where there is no quantification of the frequency with which medical progress relies on research on humans – just that it ultimately can – and the English where it must. In the Spanish there is quantification indicating that "many times" this necessity occurs. However it does not carry the "must" of the English version. Interestingly, the 1996 version of this paragraph in Spanish is closer to the English version stating that medical progress "should ultimately be based in part on research on humans".

Back translations:

(1) The development of medicine is based on research, which, as a last resort, needs to resort to experimentation with human beings.

(2) The progress of medicine is based on research, which, in the last analysis, must often resort to experimentation on human beings.

(3) Medical progress is based on research, which in many cases includes human experiments.

The back translations (at least (1) and (2)) carry the meaning closer to that of the French version.

The importance of the differences in the overall meaning of the document could be argued to be minor in that the Declaration overall spells out the ethical guidelines when research is conducted on human beings. However, there may be an interesting ethical imperative arising more strongly out of the Spanish and French versions. If it is implied that it is not always necessary to conduct research on humans to advance medicine, then the imperative is implied that other ways of advancing medicine should be sought; a parallel to the concept of "replace" among the 3-Rs of animal research. If such research is inevitable, as implied by the English

version (and which is certainly the case in such types of research endeavour as the development of new drugs), then while "reductions" and "refinements" (to continue the comparison with the 3-R model) may still be achievable, replacement can never be completely achieved. We argue that this nuance of meaning difference is important and ways should be sought to bring the meaning of the 3 versions closer together.

Paragraph 5

English version (2000): In medical research on human subjects, considerations related to the well-being of the human subject should take preference over the interests of science and society.

1996 version: In the previous version of the Declaration of Helsinki a similar statement was made under two sections, viz. those pertaining to clinical and to non-clinical research. This dichotomous schematisation of research has been eliminated in the 2000 version of the Declaration of Helsinki and this particular statement has been moved to the Introduction. The following are the two paragraphs from the 1996 version:
I.5b Concern for the interests of the subject must always prevail over the interests of science and society.
III.4 In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

French version (2000): Dans la recherche médicale sur les sujets humains, les interest de la science et de la société ne doivent jamais prévaloir sur le bien-être du sujet.

1996 version: I.5b Les intérêts du sujet doivent toujours passer avant ceux de la science ou de la société.
III.4 Dans la recherche médicale, les intérêts de la science et de la société ne doivent jamais prévaloir sur le bien-être du sujet.

Differences on initial analysis:
5.1F This is a striking difference between the two versions. In both cases there was the option to choose between the positively worded ("should take precedence") option which has made its way into the English version and the negatively worded ("must never prevail over") option which has made its way into the French version.

Back translation:

(1) In medical research on human subjects, the interests of science and society must never prevail over the well-being of the subject.

(2) In medical research on human subjects, the interests of science and society must never prevail over the well-being of the subject.

(3) In medical research on human subjects, the interests of science and of society must never infringe upon the well-being of the human subject.

All 3 back-translations not surprisingly retain this form. This is an unnecessary difference as the negation could have been chosen for the English as well. The French version, when rendered in English, sounds like a much stronger statement of protection; it is a prohibition with a stronger sound "must never" as opposed to the rather weaker sounding "should always" of the official English version. Even if the French were to translate into "should never", the sense of prohibition phrased in the form of a negative seems to give a stronger sound to this principle.

Spanish version (2000): En investigación médica en seres humanos, la preocupación por el bienestar de los seres humanos debe tener siempre primacía sobre los intereses de la ciencia y de la sociedad.

1996 version: I.5b La preocupación por el interés del individuo debe siempre prevalecer sobre los intereses de la ciencia y de la sociedad.
III.4 En la investigación en seres humanos, nunca debe dares preferencia a los intereses de la ciencia y de la sociedad, antes que al bienestar del individuo.

Differences on initial analysis:

5.1S In English 'should take precedence' is rendered in Spanish as 'debe tener siempre primacia' which literally is 'should <u>always</u> take precedence'.

Back translations:

(1) In medical research on human beings, the concern for the welfare of human beings must have primacy over the interests of both science and society.

(2) In medical research on human beings, the concern for the well-being of human beings must always have primacy over the interests of science and society.

(3) In human medical research, an individual's welfare must be taken as the first priority, above the interest of science and society.

The perceived difference in 5.1S disappears in all of the back translations.

All three back translations preserve the positive form of the statement so in this regard the Spanish version has followed the English version. See comments above regarding the differences here. If the aim of minimising any unnecessary differences between the 3 official versions is to be met, a decision should be made as to which format should be used and that format applied to all 3 language versions.

Paragraph 6

English version (2000): The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

1996 version: The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease. (para 3 of Introduction)

French version (2000): L'objectif essentiel de la recherche médicale sur des sujets humains doit être l'amélioration de méthodes diagnostiques, thérapeutiques et de prévention, ainsi que la compréhension des causes et des mécanismes des maladies. Les méthodes diagnostiques, thérapeutiques et de prévention, même les plus éprouvées, doivent constamment être remises en question par des recherches portant sur leur efficacité, leur efficience et leur accessibilité.

1996 version: L'objet de la recherche biomédicale sur des sujets humains doit être l'amélioration des méthodes diagnostiques, thérapeutiques et prophylactiques, et la compréhension de l'étiologie et de la pathogenèse.

Differences on initial analysis:
6.1F One of the most striking differences between the English and the French versions of the Declaration of Helsinki is the omission from the French version of the word qualité (quality) from the list of the 4 criteria by which even the best proven methods must continuously be challenged through research.

6.2F The English version uses the word order "prophylactic, diagnostic and therapeutic methods" whereas the French version uses "diagnostic, therapeutic and prophylactic". Additionally the word "prophylactiques" from the 1996 French version has been changed to read "prévention" whereas the English retains "prophylactic".

Back translations:

(1) The essential purpose of medical research on human subjects must be the improvement of preventive diagnostic [sic], therapeutic and preventive methods, as well as the understanding of the causes and the mechanisms of diseases. The diagnostic, therapeutic and preventive methods, even the best-tried, must be constantly challenged through research on their effectiveness, their efficiency and their accessibility.

(2) The essential objective of medical research on human subjects must be the improvement of diagnostic, therapeutic and preventive methods, as well as the understanding of the causes and mechanisms of illnesses. Diagnostic, therapeutic and preventive methods, even the most proven ones, have to be constantly challenged by research into their effectiveness, efficiency and accessibility.

(3) The primary objective of medical research on human subjects must be the improvement of diagnostic, therapeutic and preventative methods, as well as the understanding of the causes and mechanisms of illnesses. The diagnostic, therapeutic and preventative methods, even the most proven, must continuously be tested through research for their effectiveness, efficiency, and their accessibility.

6.1F All 3 of the back-translations confirm the absence of 'quality' as might be expected. Discussions with Professor Detilleux led to the conclusions that what was perceived as the very broad and ill-defined nature of the word led to the decision by the Francophone countries to omit the word. However, it is important to consider what may be lost in doing so. For example, the word 'safety' is not among the criteria listed in the Declaration of Helsinki. If the notion of 'safety' is partly subsumed within the notion of quality, then its omission may be risky. In any case, in the absence of any major difference in meaning between the 4 criteria words within the research context in French or English, the omission is difficult to justify if the aim is that the documents be as close as possible to one another.

6.2F The order of the words and the change to the word "prévention" are retained in the back translations. Some could argue that the order of the words is a stylistic choice and does not really matter. However, given the notion that trying to prevent illness should come first (both in a temporal sense and in order of priority), then comes diagnosis and then treatment as a natural progression, then the use of 'prophylactic' first has some basis in logic. There seems no reason to have a difference between the two versions. Regarding the change from prophylactic to prevention, the two words are essentially synonymous but the word "prevention" represents plainer English while the word "prophylactic" seems more like medical jargon.

Spanish version (2000): El propósito principal de la investigación médica en seres humanos es mejorar los procedimientos preventivos, diagnósticos y terapéuticos, y también comprender la etiología y patogenia de las enfermedades. Incluso, los mejores métodos preventivos, diagnósticos y terapéuticos disponibles deben ponerse a prueba continuamente a través de la investigación para que sean eficaces, efictivos, accesibles y de calidad.

1996 version: El proposito de la investigación biomédica en seres humanos debe ser el mejoramiento de los procedimientos diagnosticos, terapeuticos y profilácticos, y la comprensión de la etiologia y patogénesis de una enfermedad.

Perceived differences on initial analysis:
6.1S English gives "the primary purpose" while Spanish uses "El propósito principal" when describing purpose of medical research. These could be rendered closer to one another by changing the English to "the principal purpose" or the Spanish to "El propósito principio". This adjective was added in the 2000 revision.

6.2S The English version reads "even the best proven" while the Spanish reads "disponibles" which translates more closely as 'available' rather than 'proven'.

Back translations:

(1) The main aim of medical research on human beings is to improve the preventive, diagnostic and therapeutic mechanisms and also to understand disease aetiology and pathogenia [sic]. Furthermore, the best preventive, diagnostic and therapeutic mechanisms available must be tested continually through research so that they are efficient, effective, accessible and of high quality.

(2) The main purpose of medical research on human beings is to improve preventive, diagnostic and therapeutic procedures, and also to understand the etiology and pathogenesis of illnesses. Also the best preventative, diagnostic and therapeutic methods available must be continually put to the test through research so that they are efficacious, effective, accessible and of quality.

(3) The main purpose of human medical research is to improve preventive, diagnostic, and therapeutic procedures. Moreover it tries to understand the etiology and pathogenesis of diseases. Even the best preventive, diagnostic and therapeutic methods available must be tested continually for their efficiency, effectiveness, accessibility and quality.

6.1S Interestingly all of the back-translations use the adjective 'main' which is synonymous in this context with 'principal'. Here there is arguably a difference in meaning. 'Primary', while it can have the same connotation as 'principal' also carries a semantic element of 'first'. Given that there is a freely available and acceptable Spanish adjective available ('primario'), or the meaning in English if 'primary' were used would not change it seems the two versions could be closer to one another. The question really is the need for an adjective at all since if this is the 'primary' purpose of medical research, what is the 'secondary' purpose or if this is the 'principal' reason, what are the 'subsidiary' reasons?

6.2S The change from the English "Even the best proven must continually be challenged" to the Spanish "even the best available should continuously be challenged" is validated by all three back-translations. 'Best proven' has, potentially, a more global sense to it than 'best available'. Although the latter could be stretched to mean 'best available anywhere in the world', that requires more semantic input and assumption that would be required with 'best proven' where no localisation is implied at all. 'Available' tends to carry with it a sense of 'on hand'. This important difference is discussed further below in 29.1S. In the context of this paragraph it is important to note that one of the criteria by which methods are to be assessed is according to their 'accessibility'. While it is true that something may be 'available' but not 'accessible', it is more glaringly obvious that something might be 'proven' but not 'accessible'. Therefore, since research into accessibility is a requirement, the contrast is thrown into sharper light if the word 'proven' is chosen.

Finally, it is interesting that all three back-translators have opted to translate 'continuamente' as 'continually' rather than 'continuously'. This change in the English version would constitute an improvement as it is the notion of continually (i.e. habitually) rather than continuously (24 hours a day without ceasing) that seems to reflect the intent of this paragraph.

Paragraph 7

English version (2000): In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

1996 version: In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

French version (2000): Dans la recherche médicale comme dans la pratique médicale courante, la mise en œuvre de la plupart des méthodes diagnostiques, thérapeutiques et de prévention expose à des risques et à des contraintes.

1996 version: Dans la pratique médicale courante, toute méthode diagnostique, thérapeutique ou prophylactique comporte des risques: ceci s'applique spécialement à la recherche biomédicale.

Perceived differences on initial analysis:
7.1F The English version uses 'and' where the French uses 'comme' which would be translated as 'like' or 'as in'.

Back translations:

(1) In medical research, as well as in standard medical practice, the implementation of most diagnostic, therapeutic and preventive methods involves risks and constraints.

(2) In medical research as in common medical practice, the implementation of most diagnostic, therapeutic and preventive methods exposes oneself to risks and constraints.

(3) In current medical research as in medical practice, implementation of most of the diagnostic, therapeutic and preventative methods, are exposed to both risks and constraints.

7.1F The back translations maintain this difference which makes no difference to meaning. Arguably either language could change so that the versions could be closer to one another.

An interesting point is the use of the word 'contraintes' in the French version which is translated as 'constraints' by all 3 translators. There is apparently no word in French which provides an equivalent of the word 'burden' in the English version.

Spanish version (2000): En la práctica de la medicina y de la investigación médica del presente, la mayoría de los procedimientos preventivos, diagnósticos y terapéuticos implicans algunos riesgos y costos.

1996 version: En la prática actual de la medicina, la mayoria de los procedimientos diagnósticos, terapéuticos y profilácticos involucran riésgos: esto se aplica especialmente a la investigación biomédica.

7.1S The Spanish version would translate into English that medical practice and research "imply some risks and costs" as compared with the English "involve risks and burdens". The question is whether the word 'costos' in Spanish and the word 'burden' in English mean the same thing and whether there is a closer equivalent.

There is a tendency in the word 'costos' to imply financial disadvantage whereas of course 'burden' has a much broader applicability.

Back translations:

(1) In current medical practice and medical research, most preventive, diagnostic and therapeutic mechanisms entail some risks and costs.

(2) In the practice of medicine and current medical research, the majority of preventative, diagnostic and therapeutic procedures involve some risk and cost.

(3) The majority of preventive, diagnostic and therapeutic procedures imply some risks and burdens in contemporary medical practice and research.

7.1S Two of the back-translations stick with the narrow translation 'cost' whereas one reads into the word 'costos' the broader word 'burden'. It is therefore plausible that the Spanish word 'costos' has the wider implication but it is also evident from two of the back translations that this may not be immediately apparent. However, it is not clear that there is a more appropriate word in Spanish that would more adequately translate as 'burdens', nor is it the intent of the paragraph to narrow the meaning to financial implications so it is probably not warranted to consider rendering the English as 'costs'. This is one of the perceived differences which apparently exists but which is necessitated by the fact that the two languages cannot be mapped exactly onto one another.

It is also very interesting to note that the Spanish version has chosen to change from 'profilácticos' in 1996 to 'preventivos' in 2000, thus coinciding with the French in this regard. This, it could be argued, strengthens our point from Paragraph 6 that the English version may be improved with the less jargonistic 'preventative' instead of the current 'prophylactic'.

Paragraph 8

English version (2000): Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognised. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

1996 version: No equivalent; this material is new to the 2000 version.

French version (2000): La recherche médicale est soumise à des normes éthiques qui visent à garantir le respect de tous les êtres humains et la protection de leur santé et de leur droits. Certaines catégories de sujets sont plus vulnérables que d'autres et appellent une protection adaptée. Les besoins spécifiques des sujets défavorisés au plan économique comme au plan médical doivent être identifiés. Une attention particulière doit être portée aux personnes qui ne sont pas en mesure de donner ou de refuser elles-mêmes leur consentement, à celles qui sont susceptibles de donner leur consentement sous la contrainte, à celles qui ne bénéficieront pas personnellement de la recherche et à celles pour lesquelles la recherche est conduite au cours d'un traitement.

1996 version: No equivalent.

8.1F The French version, in the 1st sentence uses 'visent à garantir' where the English uses 'promote' with respect to the duty to respect the health and rights of human beings. The French version would more readily translate into the English 'seek to guarantee'.

8.2F 'Plus vulnérables que d'autres' is used in the French which would translate 'more vulnerable than others' whereas the English version simply states 'are vulnerable'.

8.3F The French version uses 'traitement' in the final sentence which would translate more closely into English as 'treatment'. The English version uses the broader word 'care' for which the French word 'soins' would be a closer translation.

Back translations:

(1) Medical research is subject to ethical norms which aim to guarantee the respect of all human beings and the protection of their health and rights. Some categories of subjects are more vulnerable than others and require specific protection. The particular needs of disadvantaged subjects, whether economically or medically, must be identified. Particular attention must be given to people who are not in a position to give or refuse consent themselves, to those who are likely to give their consent under constraint, to those who will not benefit from the research on a personal level and to those for whom research is conducted during treatment.

(2) Medical research is subjected to ethical norms that aim at insuring respect for all human beings and protection of their health and rights. Some categories of subjects are more vulnerable than others and call for adapted protection. The specific needs of subjects who are economically or medically disadvantaged

have to be identified. Special attention has to be given to people who are not able to give or refuse their consent themselves, who are susceptible to give their consent under constraint, who will not personally benefit from the research and to those for whom the research is conducted during a treatment.

(3) Medical research is subject to ethical standards that aim to guarantee respect for all human beings and to protect health and rights. Certain subject categories are more vulnerable than others and call for special protection. The special needs of subjects that are at an economic and medical disadvantage must be recognised. Special attention must be brought to those who cannot give or refuse consent for themselves, to those that are susceptible to give their consent under duress, to those who will not personally benefit from research, and to those for whom the research runs alongside medical care.

8.1F The back translations retain the difference between the two and capture the note of aiming at insuring or guaranteeing the respect for human health and rights. This seems to be a stronger statement than is incorporated in 'promote'. The two versions are not as close as they could be and given the importance of what is at stake – i.e. the health and rights of human beings participating in research, it would seem that the stronger French form should be favoured and the English amended accordingly.

8.2F The difference between 'are more vulnerable than others' and simply 'are vulnerable' persists with all 3 of the back-translations. It would seem simply that the French version has captured the point at stake more clearly. By spelling out the risks and burdens inherent in all medical practice and research, Paragraph 7 leads to a reasonable conclusion that to some extent all human subjects in research are vulnerable. It is the fact that some groups are more vulnerable than others that is the salient point. The two versions are not as close as they could be and we believe the French version to be superior.

8.3F Two of the back translations retain 'treatment' whereas one uses the word 'care'. Therefore, this would seem to indicate the possibility of a reasonable amount of semantic overlap. This is the first occurrence in the Declaration of the choice of the word 'traitement' in French where the word 'care' is used in English. 'Care' of course is a much broader notion than 'treatment'. The word 'soins' is available in French to reflect more closely the English rendering 'traitement'.

Spanish version (2000): La investigación médica está sujeta a normas éticas que sirven para promover el respeto a todos los seres humanos y para proteger su salud y sus derechos individuales. Algunas poblaciones sometidas a la investigación son vulnerables y necesitan protección especial. Se debe reconocer las necesidades

particulares do los que tienen desventajas económicas y médicas. También se debe prestar atención especial a los que no pueden otorgar o rechazar el consentimiento por sí mismos, a los que pueden otorgar el consentimiento bajo presión, a los que no se beneficiarán personalmente con la investigación y a los que tienen la investigación combinada con la atención médica.

1996 version: No equivalent.

Perceived differences on initial analysis:
8.1S The phrase 'ethical standards' in English is translated as 'normas eticas' (closer equivalent in English = 'ethical norms').

8.2S The phrase 'combined with care' (English) occurs as 'combinada con la atencion medica' in Spanish which would translate as 'combined with medical attention'.

Back translations:

(1) Medical research is subject to ethical norms for promoting the respect of all human beings and safeguarding both their health and individual rights. Some populations undergoing research are vulnerable and therefore need special protection. The particular needs of those with economic and medical disadvantages must be acknowledged. Also, special attention must be addressed to those who can not give or reject their consent by themselves, to those who are liable to give their consent under pressure, to those who will not benefit personally from research and to those subject to research combined with medical care.

(2) Medical research is subject to ethical standards that promote respect for all human beings and protect the health and rights of the individual. Some populations subjected to research are vulnerable and need special protection. It is necessary to recognise the particular needs of those who have medical or economic disadvantages. Also it is necessary to pay special attention to those who cannot themselves give or withhold consent, to those that give consent under pressure, to those that will not benefit personally from the research and those who have research combined with medical attention.

(3) Medical research must follow ethical rules to promote respect for all human beings and to protect their health and individual rights. Some populations under research are vulnerable and need special protection: People with economic and medical disadvantages, those who have an inability to give or to refuse their own consent or those who are under pressure to give consent need special attention, as do patients who will not benefit personally from the research or where research is combined with medical attention.

8.1S One back translation uses 'norms', one uses 'standards', and one uses 'rules' in translating 'normas eticas'. The semantic overlap is considerable and although it the case could be argued for wording which made them more exactly equivalent, the fact that at least one translator spontaneously uses the word 'standards' (Eng.) for 'normas' (Sp.) weakens the claim that this is an important difference.

8.2S Two back translations strictly adhere to 'medical attention' as the translation of 'atencion medicale' whereas one uses 'medical care'. While there remains an argument that a more precise equivalence between phrases would be possible, there is really no difference in meaning. Certainly the notion of 'attention' is closer to the full range implied by 'care' than would be implicit in the more specific idea of 'treatment'.

Paragraph 9

English version (2000): Research investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this document.

1996 version: It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries. (para 8b from Introduction)

French version (2000): L'investigateur doit être attentif aux dispositions éthiques, légales et réglementaires applicables à la recherche sur les sujets humains dans son propre pays ainsi qu'aux règles internationales applicables. Aucune disposition nationale d'ordre éthique, légal et réglementaire ne doit conduire à affaiblir ou supprimer les mesures protectrices énoncées dan la présente déclaration.

1996 version: Il est souligné que ces règles ont été rédigées seulement pour éclairer la conscience des médecins du monde entier. Ceux-ci ne sont pas exemptés de leur responsabilité pénale, civile et déontologique à l'égard des lois et des règles internes de leur propre pays.

9.1F 'Supprimer les mesures protectrices' (Eng. = remove protective measures) was seen as potentially different from 'eliminate any protective measure'.

Back translations:

(1) The investigator must pay attention to the ethical, legal and statutory arrangements applicable to research on human subjects in his/her country, as well as to the international rules applicable. No national arrangements, whether ethical, legal or statutory, should lead to the weakening or the suppression of protective measures stated in the present declaration.

(2) The investigator has to be cautious regarding the ethical and legal provisions and regulations applicable to research on human subjects in his country, as well as the international applicable rules. No ethical or legal national provision or regulation should lead to the weakening or the suppressing of the protective measures stated in this declaration.

(3) The Researcher must be aware of the ethical, legal and regulatory requirements for research on human subjects in their own country, as well as any additional international requirements which may be applicable. No national ethical, legal or regulatory requirement must be allowed to reduce or eliminate the protective measures for human subjects declared by this Declaration.

None of the back translations renders this as eliminate – but then also none of them use 'remove'. Two have used 'suppress' and one 'eliminate'. The semantic range is blurred and it is difficult to persist in any objection to the wording 'supprimer les mesures'.

Spanish version (2000): Los investigadores deben conocer los requisitos éticos, legales y judicos para la investigación en seres humanos en sus propios países, al igual que los requisitos internacionales vigentes. No se debe permitir que un requisito ético, legal o juridico disminuya o elimine cualquiera medida de protección para los seres humanos establecida en esta Declaración.

1996 version: Para. 8b from introduction – Debe enfatizarse el hecho de que los estándares diseñados son sólo una guía para los médicos de todo el mundo. Los medicos no están exentos de la responsabilidad en lo civil, ético, y criminal bajo las leyes de sus propios países.

9.1S Protections for human subjects are 'set forth' in the English version whereas they are 'establiceda' (established) in the Spanish version.

Back translations:

(1) Researchers must be aware of the ethical, lawful and legal requirements for research on human beings in their own countries, as well as the international requirements currently in force. It can not be allowed that an ethical, lawful

or legal requirement decreases or eliminates any form of protection for human beings set out in this Declaration.

(2) Researchers must know the ethical, legal and juridical requirements for research on human beings in their own countries and the same for the international requirements in force. No ethical, legal or juridical requirements may be allowed to weaken or remove any means of protecting human beings established in this Declaration.

(3) Researchers must be aware of ethical, legal and juridical requirements for human research within their own countries and internationally. Any ethical, legal or judicial requirement must not be allowed to decrease or eliminate any protective measure established in this Declaration.

9.1S One of the back translators has in fact rendered 'establiceda' as 'set forth'. The other two back translators use 'established'. It could be argued that a more precise equivalence may be achieved by using the word 'established' in English. There is an interesting potential difference in meaning between the two which should be discussed here. What does the Declaration do? Does it 'establish' or 'set forth' the ethical guidelines? Clearly the act of 'establishing' the guidelines is a more profound event than 'setting forth'. In the latter case, already existent principles are expounded. The former *creates* the principles. This important philosophical concept relates to just what occurs when an authoritative body develops an ethical code. The argument will not be developed further here but rather this will simply be used as example of where the requirement for as precise a possible translation is justified and seemingly innocuous differences can actually represent significant changes in meaning.

B. Basic Principles For All Medical Research (Paragraphs 10-27)

Paragraph 10

English version (2000): It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

1996 version: . In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

French version (2000): Dans la recherche médicale, le devoir du médecin est de protéger la vie, la santé, la dignité et l'intimité de la personne.

1996 version: III.1 Dans l'application d'expériences purement scientifiques enterprises sur l'homme, le devoir du médecin est de rester le protecteur de la vie et de la santé du sujet de l'expérience.

10.1F There is a difference in word order here; the French version begins with the phrase "In medical research, the duty of the physician..." whereas the English says "It is the duty of the physician in medical research...". This is stylistic only and does not lead to any difference in meaning.

Back translations:

(1) In medical research, the duty of the physician is to protect the life, health, dignity and privacy of the person.

(2) In medical research, the duty of the doctor is to protect the life, health, dignity and privacy of the person.

(3) In medical research, the duty of the physician is to protect the life, health, dignity and privacy of the human subject.

The word order change is perpetuated in back translation but seems to be of no semantic significance. Arguably the French version could be said to be emphasising the setting, i.e., "In medical research" whereas the English emphasises the duty of the physician.

Spanish version (2000): En la investigación médica, es deber del médico proteger la vida, la salud, la intimidad y la dignidad del ser humano.

1996 version : Es responsabilidad del médico el permanecer como protector de la vida y la salud de la persona en quien se lleva a cabo la investigación mientras se desarrolla la investigación médica en la aplicación puramente científica.

10.1S The word order corresponds to that in the French version in contrast to the English version.

Back translations:

(1) In medical research, it is the doctor's duty to safeguard life, health, privacy and dignity of any human being.

(2) In medical research, it is the duty of the doctor to protect the life, health, privacy and dignity of the human being.

(3) In medical research, doctors must protect human life, health, privacy and dignity.

The difference persists with back translation. As discussed above the difference is largely stylistic.

Paragraph 11

English version (2000): Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

1996 version: Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

French version (2000): La recherche médicale sur des êtres humains doit se conformer aux principes scientifiques généralement reconnus. Elle doit se fonder sur une connaissance approfondie de la littérature scientifique et des autres sources pertinentes d'information ainsi que sur une expérimentation appropriée réalisée en laboratoire et, le cas échéant, sur l'animal.

1996 version: I.1 La recherche biomédicale portant sur des êtres humains doit être conforme aux principes scientifiques géneralement reconnus et doit être basée sur une expérimentation réalisée en laboratoire et sur l'animal, exécutée de manière adéquate, ainsi que sur une connaissance approfondie de la littérature scientifique.

11.1F The French phrase 'le cas échéant' translates 'if need be' which appears to differs slightly from the English 'where appropriate' with respect to the conditional clause applying to information from animal experimentation. The phrase 'if need be' would appear to be a stronger restriction – along the lines of 'if there is no other way' whereas the word 'appropriate' allows for broader interpretation. The difference in meaning, however, if valid is slight.

Back translations:

(1) Medical research on human beings must conform to the generally recognised scientific principles. It must be based on a thorough knowledge of scientific literature and other relevant sources of information, as well as on appropriate experimentation carried out in laboratories, and if need be, on animals.

(2) Medical research on human beings must conform to the scientific principles that are generally accepted. It has to be based on a thorough knowledge of

scientific literature and other relevant sources of information as well as an appropriate experimentation made in a laboratory and, if need be, on animal subjects.

(3) Medical research carried out on human subjects must conform to scientific principles which are generally recognised. It must be founded on thorough knowledge of scientific literature and other sources of pertinent information as well as on appropriate laboratory experimentation, and where appropriate, through animal experimentation.

11.1F The fact that only 2 of the back translations use 'if need be' and the 3rd renders this as 'where appropriate' seems to indicate that there is potential semantic overlap. Perhaps it is too fine a distinction to be of any importance. On the other hand, either of the versions could quite simply be changed to be a more exact translation though probably the ethical notion is best captured by the phrase 'if need be' as opposed to the arguably more wishy-washy 'where appropriate'.

Spanish version (2000): La investigación médica en seres humanos debe conformarse con los principios cientificos generalmente aceptados, y debe apoyarse en un profundo concocimiento de la bibliografia científica, en otras fuentes de información pertinentes, así como en experimentos de laboratorio correctament realizados y en animales, cuando sea oportuno.

1996 version: L'investigación biomedica que involucra a sujetos humanos debe atenerse a los principios científicos aceptados en general y deberían basarse en experimentaciones de laboratorio y en animales realizadas adecuadamente y en un amplio conocimiento de la literatura cientifica.

11.1S Here the English uses 'must conform' and the Spanish 'debe'. This is one of the situations where the absence of distinction within the meaning of 'debe' – it can mean either – shows itself. There is no real problem with meaning. However, it could be argued that the English text could be tidied up by deciding on and sticking to either 'must' or 'should' (we prefer 'should') to avoid any confusion.

11.2S Here the Spanish phrase 'cuando sea oportuno', the equivalent of 'where appropriate' applies, because of the way the sentence is constructed to both laboratory experiments and animal experiments.

Back translations:

(1) Medical research on human beings must comply with the scientific principles generally accepted, and must be based on a thorough knowledge of scientific bibliography, other relevant sources of information, as well as on laboratory experiments correctly used and on animals, where appropriate.

(2) Medical research on human beings must conform with generally accepted scientific principles and must be supported by a deep knowledge of scientific literature, in other sources of relevant information such as laboratory experiments correctly carried out on animals, when it is opportune.

(3) Human medical research must be in accordance with widely accepted scientific principles. Human medical research must be based on a thorough knowledge of the scientific literature and in other relevant sources of information as well as acceptable animal and laboratory experiments, where appropriate.

11.1S The back translations use 'must' in this situation and this corresponds with the English version.

11.2S The back translations preserve the application of 'where appropriate' to laboratory and animal experiments in 2 cases and in the 3rd there is a conflation of the two concepts resulting in the phrase 'laboratory experiments correctly carried out on animals'. Since there seems to be some intention to give special emphasis on the need to consider the appropriateness of animal experiments (as requiring additional ethical considerations over and above literature review, laboratory experiments and so forth), the two versions could be brought closer to one another with the wording: 'y en experimentos de laboratorio correctamente realizados y cuando sea oportuno, experimentos en animals'.

Paragraph 12

English version (2000): . Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

1996 version: Special conduct must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

French version (2000): Des précautions particulières doivent entourer les recherches pouvant porter atteinte à l'environnement et le bien-être des animaux utilisés au cours des recherches doit être préservé.

1996 version: (Para 7) Des précautions spéciales doivent être prises dan la conduite de recherches pouvant porter atteinte à l'environnement. Le bien-être des animaux employés au cours des recherches doit être protégé.

No particular differences between the English and French versions were identified on initial analysis.

Back translations:

(1) Particular precautions should surround research which may affect the environment and the well-being of animals used for research must be preserved.

(2) Special precautions must be taken with research that may damage the environment. The well-being of the animals that are used during research must be preserved.

(3) Necessary precautions must be carried out with any research that may affect the environment and the well-being of animals utilised during research must be respected.

The back translations seem to bear out the fact that no particular differences exist. One translator has put her own 'gloss' on the translation of 'pouvant porter atteinte l'environment' by using the word 'damage' in the back translation when the original phrase probably connotes a more neutral term 'affect'. Interestingly, the Spanish version (below) uses a term with a negative connotation 'perjudicar' in this context. The back translation of 'préservé' as 'preserved' by 2 back translators and 'respected' by the 3rd probably justifies not identifying this as a potential difference between the two in the initial analysis.

Spanish version (2000): Al investigar, hay que prestar atención adecauda a los factores que puedan perjudicar el medio ambiente. Se debe cuidar también del bienestar de los animals utilizados en los experimentos.

1996 version: Debe prestarse especial atención en la conducción de investigaciones que puedan afectar al medio ambiente, y deberá respetarse el bienestar de los animals utilizados para la investigación.

12.1S The Spanish version uses 'cuidar' ("cared for") where the English uses 'respected' regarding the well-being of animals used in research.

Back translations:

(1) When researching, one must draw special attention to the factors that can damage the environment. The welfare of the animals used in experiments must also be safeguarded.

(2) To research, it is necessary to pay adequate attention to the factors that can harm the environment. One should also look after the well-being of animals used in experiments.

(3) In research, attention must be paid to any factors that could harm the environment. In animal experiments, the welfare of animals must be protected.

12.1S Three different phrases emerge from the back-translations: 'safeguarded', 'look after' and 'protected'. Although the specific word 'respetado' would have been available in Spanish it is probably "splitting-hairs" to try to argue, especially given the variety within the back-translations, that the use of 'cuidar' results in a different meaning from 'respected'.

Paragraph 13

English version (2000): The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

1996 version: I.2 The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

French version (2000): La conception et l'exécution de chaque phase de l'experimentation sur des sujets humains doivent être clairement définies dans un protocole expérimental. Ce protocole doit être soumis pour examen, commentaires, avis et, le cas échéant, pour approbation, à un comité d'éthique mis en place à cet effet. Ce comité doit être indépendant du promoteur, de l'investigateur ou tout autre forme d'influence indue. Il doit respecter les lois et règlements en vigueur dans le

pays où s'effectuent les recherches. Il a le droit de suivre le déroulement des études en cours. L'investigateur a l'obligation de fournir au comité des informations sur le déroulement de l'étude portant en particulier sur la survenue d'événements indésirables d'une certaine gravité. L'investigateur doit également communiquer au comité, pour examen, les informations relatives au financement, aux promoteurs, à toute appartenance à une ou des institutions, aux éventuels conflits d'intérêt ainsi qu'aux moyens d'inciter des personnes à participer à une recherche.

1996 version: I.2 Le projet et l'exécution de chaque phase de l'expérimentation portant sur l'être humain doivent être clairement définis dan un protocole expérimental qui doit être soumis pour examen, commentaire et conseil à un comité dèsigné spécialement à cet effect, indépendant du chercheur et du sponsor, à condition que la création de ce comité indépendant soit conforme aux lois et règlements en vigeur dan le pays où s'effectuent les recherches expérimentales.

13.1F The words 'chaque phase' (Fr.) give rise to particular concern here. The English version uses 'any human experimental procedure'. In the context of medical research 'phase' has come to have some specific meaning with respect to the process of drug development, i.e. Phase I-IV trials. There is potential, on reading the French version, to take it to mean that each of these phases requires formulation in a protocol for approval.

13.2F Again 'le cas échéant' ('if need be') is used when English uses 'where appropriate'. Here perhaps the difference is less of a problem than in 11 (see above) in that usually where it is appropriate to get ethical committee approval is where local law or regulation requires it in which case 'if need be' applies as well!

13.3F The sentence division differs between the two versions. In the French version uses a separate sentence to express the notion of the committee's independence from the investigator, the sponsor or any other undue influence. Since this expresses a separate thought, this seems preferable to the unduly long English sentence. The meaning, however, is unchanged.

13.4F There is a change in word order in one sentence (for no obvious reason as the meaning appears unchanged): '...committee, which must be independent of the investigator, the sponsor or any other kind of...' (Eng.) appears in French as 'comité doit être independent du promoteur, de l'investigateur ou de tout autre forme...'.

13.5F The French version uses the pronoun 'il' where the English repeats the noun 'This independent committee'. This appears to be stylistic in nature. It may relate to the choice in 13.3F to divide sentences differently. The use of the pronoun in French avoids beginning two consecutive sentences with 'ce comité'.

13.6F The use of 'certaine gravité' is used in French where 'serious' is used in English as the adjective describing the particular importance of notifying certain events to the ethical review committee.

13.7F The use of 'appartenance' (Eng. = membership) in French relating to institutions where the English version uses 'affiliation'. While it could be argued that these constitute different categories of relationships to an institution, this would seem to be splitting hairs as the meaning is quite clear.

Back translations:

(1) The conception and the execution of each phase of the experimentation on human beings must be clearly defined in an experimental protocol. This protocol must be examined by an ethics committee (set up to that effect) which will give its commentaries and opinion, and if need be, its approval. This committee must be independent from the instigator, the investigator or any other kind of undue influence. The committee must respect the laws and rules in force in the country where the research is carried out. The committee has the right to follow the progress of the studies under way. The investigator must provide the committee with information on the progress of the study, in particular on the occurrence of undesirable events of some seriousness. The investigator must also present to the committee, for examination, information detailing financing, instigators, memberships to one or several institutions, possible conflicts of interest and the methods used to encourage people to partake in any research.

(2) The conception and execution of each phase of the experimentation on human beings must be clearly defined in an experimental protocol. This protocol must be submitted for examinations, comments, opinion and, if the need arises, for approval to an ethical committee set for this purpose. This committee must be independent of the promoter, the investigator or any form of undue influence. It has to respect the laws and rules in force in the country where research is carried out. The committee is entitled to follow the development of the studies under way. The investigator is obliged to provide the committee with information on the development of the studies, in particular information on the occurrence of undesirable events of any gravity. The investigator must also communicate to the committee, for examination purposes, information relating to funding, to the promoters, to membership of any institution, to possible conflicts of interest as well as to means of encouraging people to participate in research.

(3) The design and performance of each phase of experimentation on human subjects must be clearly defined in an experimental protocol. This protocol must be submitted for examination, commentary, opinion and, if the case

arises, for approval to an ethical review committee joined together for this sole purpose. This committee must be independent of the sponsor, the investigator or of all other forms of undue influence. It must conform to the existing laws of the country where the research is being carried out. The committee has the right to follow the process of the research project. The investigator must provide the committee with all information on the progress of the study, particularly of any undesirable or grave events during the course of the research. The researcher must equally communicate to the committee, for review information relative to funding, sponsors, all institutional affiliations, eventual conflicts of interest as well as incentives for persons to take part in any research.

13.1F The difference between the French 'chaque phase' and the English 'each experimental procedure' is borne out by the back translations. In each of the above back translations, there is potential confusion and, since the intent is not approval be sought for all phase I studies or all phase III studies regarding a particular drug for example it would seem preferable to use the phrase 'chaque procédure expérimentale'.

13.2F Again the difference between 'les cas échéant' and 'where appropriate' is borne out by the back translations. It seems a less important difference here than with regard to the statement in Paragraph 11. However, because there is not complete identity between the two situations – i.e., 'if need be' always implies 'appropriate', but there may be situations where ethical approval would be considered appropriate (from an ethical perspective) but perhaps not specifically required by the law of the land (which may be what is envisaged by 'if need be') there may be a case for suggesting that 'où semble approprié' be used instead.

13.3F The back translations, not surprisingly, preserve the different sentence divisions.

13.4F The back translations preserve the change in word order between investigator and sponsor. While there is no difference in meaning, this is an unnecessary difference.

13.5F It is interesting that one of the 3 back translators spontaneously inserts the noun where the French version used the pronoun. However, reading the versions with the pronoun in place it is difficult to see any way in which the pronoun introduces confusion in either the official French version or in the back-translated English versions. Therefore it is a stylistic choice as to which is used.

13.6F One of the back translations has rendered 'certaine gravité' as 'some seriousness'. There is clearly sufficient semantic overlap and the meaning is quite

clear in both. Whether the word 'sérieux' would be preferable to bring the two closer together is therefore somewhat moot. Chaging the English to 'grave' or a suitable cognate would be a somewhat awkward usage.

13.7F Two back translators used 'membership' and one used 'affiliation'. Being employed by an institution may or may not be construed as 'membership' in English (although the phrase 'members of staff' gives this a dimension of synonymity). The semantic overlap between 'membership' and 'affiliation' in this context probably negates the need to suggest that the two versions could be brought closer to one another by a change in word choice.

Spanish version (2000): El proyecto y el método de todo procedimiento experimental en seres humanos debe formularse claramente en un protocolo experimental. Este debe enviarse, para consideración, comentario, consejo, y cuando sea oportuno, aprobación, a un comité de evaluación ética especialmente designado, que debe ser independiente del investigador, del patrocinador o de cualquier otro tipo de influencia indebida. Se sobreentiende que ese comité independiente debe actuar en conformidad con las leyes y reglamentos vigentes en el país donde se realiza la investigación experimental. El comité tiene el derecho de controlar los ensayos en curso. El investigador tiene la obligación de proporcionar información del control al comité, en especial sobre todo incidente adverso grave. El investigador también debe presentar al comité, para que la revise, la información sobre financiamiento, patrocinadores, afiliaciones institucionales, otros posibles conflictos de interés e incentivos para las personas del estudio.

1996 version: I.2 El diseño y el desarrollo de cada procedimiento experimental que involucre a sujetos humanos deberiá ser claramente formulado en un protocolo experimental el cual debería ser remitido para evaluación y consideración, comentarios y guía de un comité especial independiente del patrocinador y del investigador, estando este comité acorde con las normas y regulaciones locales del país en el que se desarrolla el estudio.

13.1S Spanish uses 'todo procedimiento experimental' (lit. 'all experimental procedures') whereas English uses 'each'. This is probably of stylistic importance only. It could be argued that the notion of 'each' suggests a 'particularisation', i.e. detail on each element of a research protocol is sought. The notion of 'todo' or 'all' gives some emphasis on a comprehensiveness – i.e., no experimental procedure is to be left out of the protocol submitted for approval.

13.2S 'Consejo' in Spanish (lit. advice) becomes guidance in English. These are essentially synonymous in context in that it is probably not possible to 'guide' without 'advising' nor is it possible to 'advise' without 'guiding'.

13.3S The committee's 'right to monitor ongoing trials' (Eng.) becomes 'de controlar los ensayos en curso' which literally is 'to control ongoing trials'. This is potentially a considerable difference in meaning although it could be argued that the only reason a committee would monitor trials would be to exercise a degree of control so that the English 'monitor' implies aspects of 'control'.

13.4S 'Incentives for subjects' (Eng.) is rendered as 'e incentivos para las personas del estudio' which literally translates as 'incentives for the people of the study'. Interestingly, incentives may be given to investigators as well as to the research subjects, perhaps as an incentive for recruitment. Given that all such incentives should be examined by the independent committee, it would seem the more inclusive Spanish version would be preferable here.

Back translations:

(1) The plan and method of every experimental procedure with human beings must be drawn up clearly in an experimental protocol. This must be sent, for consideration, comment and advice, and where appropriate, for approval, to a committee for ethical evaluation specially appointed and which must be independent from the sponsors or any other improper influence. It is understood that the said independent committee must act in compliance with the current legislation and norms in force in the country where the experimental research is conducted. The committee is entitled to monitor the tests being carried out. Researchers have an obligation to provide information to the committee about the monitoring and in particular about any serious adverse incident. Researchers must also submit to the committee for examination, information on funding, sponsors, membership, and any other possible conflicts of interest and incentives for the people involved in the study.

(2) The project and the method of all experimental procedure on human beings must be clearly formulated in an experimental protocol. This must be sent, for consideration, comment, advice and when opportune, approval, to an ethical evaluation committee, designated especially, that must be independent of the researcher, the sponsor, or any other type of improper influence. It is self-evident that this independent committee must act in conformity with the laws and regulations in force in the country where the experimental research is carried out. The committee has the right to control the trials that are underway. The researcher is obliged to provide the committee with control information, especially on all serious adverse incidents. The researcher must also present the committee, for its review, information on the finances, sponsorship, institutional affiliations, other possible conflicts of interest and incentives for the people in the study.

(3) The project design and methods involved in any human experimental procedure must be clearly formulated in an experimental protocol. This protocol must be sent for consideration, comment, advice and where necessary, approval, to an ethical evaluation committee especially appointed. This committee must be independent from the researcher, sponsor or any other undue influence. This committee should be totally neutral and will act in accordance with the laws and regulations of the country where the experimental research will take place. The committee has authority over any part of the experiment. The researcher has the obligation to provide any required information to the committee and especially, information about any serious adverse incident. The researcher must provide information about finance, sponsors and institutional affiliations to the committee for auditing. The researcher must provide, as well, any other information about possible conflicts of interests and any possible incentives for people in the research.

13.1S Interestingly all 3 back translations render 'todo' differently, i.e., as 'every', 'all' and 'any'. However, the comment above regarding the difference in emphasis is retained with each of these back translations. A possible construction in Spanish would be 'El diseño y funcinamiento de cada procedimitento experimental' although this may be a somewhat awkward construction.

13.2S All 3 back translations retain 'advice'. Our comment above indicates that these seem to be synonymous. However, nothing would be lost by changing the English to 'advice' and this would render the two as more exact translations of one another.

13.3S All three back translations handle this differently; one has 'control', the other 'has authority over' and the 3rd reverts to the English 'monitor'. It could be argued therefore that there is considerable semantic overlap. The Spanish word has a broader semantic range which includes both 'monitor and control'. There is no obvious Spanish alternative which would mean 'monitor' more specifically. So although there is not a precise overlap of meaning here, this different seems to be an inevitable results of the differences in the languages.

13.4S The back translations retain the broader meaning inherent in the Spanish – it is 'people involved in the study' and not specifically the research subjects. This, as we argue above, is preferable and the English version would be rendered closer to the Spanish, and probably improved by simply stating 'incentives for people involved in the research'.

Paragraph 14

English version (2000): The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enumerated in this Declaration.

1996 version: I.12 The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

French version (2000): Le protocole de la recherché doit contenir une déclaration sur les implications éthiques de cette recherche. Il doit préciser que les principes énoncés dans la présente déclaration sont respectés.

1996 version: I.12 Le protocole de la recherche devra toujours contenir une déclaration sur les considérations éthiques impliquées dans cette recherche et devra indiquer que les principes énoncés dan la présente déclaration sont respectés.

No particular differences between the French and English versions were found on initial analysis. There is an instance here of the use of 'doit' in French where 'should' is used in English.

Back translations:

(1) The protocol of the research must contain a declaration on the ethical implications of this research. It must specify that the principles stated in the present declaration be respected.

(2) The research protocol must contain a declaration on its ethical implications. It must stipulate that the principles detailed in the present declaration are being respected.

(3) The protocol of the research must contain a statement on the ethical implications of the research. It must specify that the enunciated principles in this Declaration are respected.

Interestingly, although it was not detected on initial analysis as a difference, all of the 3 back translations have retained 'respected' whereas the English DoH uses the word 'compliance'. Given that this is a set of ethical guidelines, it would seem that 'respected' is perhaps the more appropriate term here; 'compliance' would be more apt in a legal setting.

Spanish version (2000): El protocolo de la investigación debe hacer referencia siempre a las consideraciones éticas que fueran del caso, y debe indicar que se han observado los principios enunciados en esta Declaración.

1996 version: El protocolo de investigación debería siempre contener un establecimiento de las consideraciones éticas involucradas y debería indicar que los mismos concuerdan con la presente declaración.

14.1S Whereas the English version says each protocol 'should always contain a statement of the ethical considerations involved' while the Spanish version uses 'hacer siempre referencia a' (lit. 'should always make reference to'). This appears to be largely stylistic and the meaning seems similar.

14.2S The English uses 'indicate that there is compliance with the principles enumerated in this Declaration'; Spanish 'indicar que se han observado los principios enunciados en esta Declaración' (lit. 'indicate that the principles enunciated in this Declaration have been observed'). Do these mean the same thing? First there is the potential difference between 'observation' and 'compliance'? Again, our contention would be that 'observation' is more apt in an ethical context than 'compliance' (see above). Secondly, does 'enunciate' mean the same as 'enumerate'? While the overall effect is undoubtedly the same, enunciate seems more appropriate. While the Declaration enumerates its paragraphs (1 to 32) it is by no means the case that every principle is enumerated. Some paragraphs draw on more than one principle. Other principles are addressed by several paragraphs. Effectively, therefore, the Declaration does not enumerate principles. 'Enunciate' is a better concept although there may be better words to communicate this concept.

Back translations:

(1) The research protocol must always refer to the ethical considerations regarding the case, and it must indicate that the principles stated in this Declaration have been observed.

(2) The research protocol must always make reference to ethical considerations where it is the case and must indicate that the principles set out in this Declaration have been observed.

(3) Research protocols must always refer to all ethical considerations and must indicate that the principles stated in this Declaration have been followed.

14.1S All 3 back translations retain the notion of 'reference'. While the two versions could be made more exact in their translation, there is no apparent meaning shift here.

14.2S Two of the back translations render 'enunciados' as 'stated' while one uses 'set out'. Both would seem preferable to either 'enumerated' or 'enunciated' (which in English is often used in the context of accurate pronunciation rather than anything else). 'Observado' is rendered twice as 'observed' and once as 'followed'. Both are

preferable to 'compliance'. We suggest changing the English to 'indicate that the principles set out (or 'set forth' would be suitable) in this Declaration have been respected/observed/followed. Any of these 3 would be suitable. The question arises as to whether the Spanish should be changed to 'respetados' to come closer to the French version or whether the French version could shift toward the Spanish. Both, however, are preferable to the English.

Paragraph 15

English version (2000): Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

1996 version: I.3 Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

French version (2000): Les etudes sur l'être humain doivent être conduites par des personnes scientifiquement qualifiées et sous le contrôle d'un médecin compétent. La responsabilité à l'égard d'un sujet inclus dans une recherche doit toujours incomber à une personne médicalement qualifiée et non au sujet, même consentant.

1996 version: I.3 L'expérience sur l'être humain doit être menée par des personnes scientifiques qualifiées et sous la surveillance d'un clinicien compétent. La responsabilité à l'égard du sujet de l'expérimentation doit toujours incomber à une personne médicalement qualifiée et ne peut jamais incomber au sujet lui-même s'il a donné son consentement.

15.1F English uses the description 'clinically competent' with respect to the qualifications of the person or persons supervising the well-being of human subjects. The French reads only 'compétent'. Competence would always carry an implicit notion of relevant competence. A competent nephrologist would be unlikely to be the appropriate physician to be responsible for human subjects undergoing research in anaesthetics (unless perhaps the research is looking specifically at effect on the renal system). The nephrologist may still be 'clinically competent'. If it is felt that it is necessary to laboriously spell out this point the English version should probably read 'medical person with relevant clinical competence'. Either the succinct French version (which would seem to contain this requirement implicitly) should be chosen

or, if it is not felt that the notion of 'relevance' is implicit, then both languages should use an even more expanded version such as the one described above so that all confusion is avoided. Our preference is for the succinct version.

Back translations:

(1) The studies on human beings must be led by scientifically qualified people and under the control of a competent physician. The responsibility towards a subject included in any research must always belong to a medically qualified person, and not to the subject, even if he/she agrees.

(2) Studies on the human being have to be conducted by persons who are scientifically qualified and under the control of a competent doctor. The responsibility towards a subject included in the research must always be incumbent upon a medically qualified person, not to the subject, even if he is consenting.

(3) The studies on the human subject must be carried out by scientifically qualified persons, and under the supervision of a competent physician. The responsibility regarding the subject must always be incumbent upon a qualified medical person and not upon the subject, even if the subject has given consent.

15.1F Not surprisingly, none of the back translations adds anything to the adjective 'competent'. The difference is clear and it is unnecessary and the changes described above should be considered if the two versions are to be as equivalent as possible.

Spanish version (2000): La investigación médica en seres humanos debe ser llevada a cabo sólo por personas científicamente calificadas y bajo la supervisión de un médico clínicamente competente. La responsabilidad de los seres humanos debe recaer siempre en una persona con capacitación médica, y nunca en los participantes en la investigación, aunque hayan otorgado su consentimiento.

1996 version: La investigación biomedical con sujetos humanos debería ser conducida solo por personas calificadas científicamente y bajo la supervisión de un médico clínicamente competente. La responsabilidad por la persona humana debe siempre recaer sobre alguien médicamente calificado y nunca sobre el paciente de la investigación, aún cuando el mismo haya dado su consentimiento.

15.1S Whereas the English version uses the phrase 'clinically competent medical person', the Spanish simply reads 'médico clínicament competente' (lit. 'clinically competent doctor').

15.2S The English 'research subjects' becomes 'participantes en la investigación' (lit. 'research participants') in Spanish.

Back translations:

(1) Medical research on human beings must be carried out solely by people scientifically qualified and under the supervision of a clinically competent doctor. The responsibility for the human beings must always lie with a person with medical training, and never with the research participants, even if they have given their consent.

(2) Medical research on human beings must be carried out only by persons scientifically qualified and under the supervision of a clinically competent doctor. The responsibility for the human beings must always rest with a person with medical training and never with the participants in the research, even if they have given their consent.

(3) Scientists can only carry out human clinical research under the supervision of a clinically competent doctor. Only a person with medical competence can take responsibility for human subjects' welfare. Participants in the research can never take that responsibility, even if they have given their consent.

15.1S All three back translations preserve the word 'doctor' thus preserving the difference between the two versions. Although slight, this difference is unnecessary and the phrase 'medical person' is an awkward construction in English. There seems no good reason for not using 'physician' in the English which would then render it identical with its French and Spanish counterparts.

15.2S The small difference is preserved in all back translations. Since the word 'participants' could in theory refer to more than 'subjects' (i.e. to the researchers themselves), and since the French version also uses 'subject' (i.e., 'sujet'), it may be preferable for the Spanish to read 'sujetos' in place of 'participantes'.

Paragraph 16

English version (2000): Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

1996 version: I.5a Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others.

French version (2000): Tout etude doit être précédée d'une évaluation soigneuse du rapport entre d'une part, les risques et les contraintes et d'autre part, les avantages prévisibles pour le sujet ou d'autres personnes. Cela n'empêche pas la participation à des recherches médicales de volontaires sains. Le plan de toutes les études doit être accessible.

1996 version: I.5a Avant d'entreprendre une expérience, il faut évaluer soigneusement les risques et les avantages prévisibles pour le sujet ou pour d'autres.

16.1F The English version states that the design of all studies should be 'publicly available' whereas the French states 'accessible'.

Back translations:

(1) All studies must be preceded by a careful evaluation of the connection between, on the one hand, the risks and constraints, and on the other, the foreseeable advantages for the subject or for other people. This does not prevent the participation of healthy volunteers in medical research. The plan of all studies must be accessible.

(2) Every study has to be preceded by a careful assessment of the connections between the risks and constraints on the one hand and the predictabe advantage for the subject or other persons on the other hand. This is no obstacle to healthy volunteers participating to medical research. The planning of all these studies must be accessible.

(3) All research must be preceded by a careful assessment of the possible risks and constraints on the one hand, and on the other the foreseeable benefits for the subject or others. This does not hinder the participation volunteers to the medical research. The outline of all parts of the research must be accessible to others.

16.1F The difference is preserved in all of the back translations. It seems that there is a serious difference in meaning here. What does 'accessible' mean? There is no suggestion of 'accessible' to whom? 'Publicly available' is a much more explicit requirement. Of course, which of these holds sway depends on the intent of the paragraph. If the study design is to be 'accessible' say to the research ethics committee, or regulatory agencies but not to the general public then 'accessible' (perhaps with some explanatory modification) would be correct. If study design is to

be accessible to *anyone*, then 'publicly available' is correct. As it is they do not say the same thing.

Spanish version (2000): Todo proyecto de investigación médica en seres humanos debe ser precedido de una cuidadosa comparación de los riesgos calculados con los beneficios previsibles para el individuo o para otros. Esto no impide la participación de voluntarios sanos en la investigación médica. El diseño de todos los estudios debe estar disponible para el público.

1996 version: I.5a Cada proyecto de investigación biomedical que involucre a sujetos humanos debería ir precedido de un establecimento cuidadoso de los riesgos predecibles en comparación con los beneficios esperados para el paciente o para otros.

16.1S 'Predictable risks and burdens' in English is rendered as 'riesgos calculados' in Spanish.

Back translations:

(1) Every medical research project on human beings must be preceded by careful comparison of the calculated risks against the foreseeable benefits for the individual and others. This does not prevent the participation of healthy volunteers in the medical research. The design of every study must be available to the public.

(2) Every medical research project on human beings must be preceded by a careful comparison of the calculated risks with the foreseeable benefits for the individual or for others. This does not prevent the participation of healthy volunteers in medical research. The design of all studies must be available to the public.

(3) Risks and benefits for patients or other participants must be calculated before undertaking any human medical research project. However, healthy volunteers can participate in medical research. Any study protocol must be publicly available.

16.1S One of the back translators (i.e. (3)) saw 'calculados' and 'previsibles' as sufficiently synonymous to eliminate any distinction. The other two preserved the difference. All back translated with 'risks' only – no connotation of 'burdens' was added. There seems little reason for the unnecessary differences here. Although there may be a problem with the earlier use of 'costos' for 'burdens' as discussed above, this seems preferable to leaving it out altogether if the two versions are to be as identical as possible. Additionally, the use of the both adjectives 'calculados' and

'previsibles' seems to introduce an unnecessary difference between the translations. It is the foreseeable-ness that is the emphasis here and we suggest that the adjective 'previsibles' be used for both 'beneficios' and 'riesgos' in the Spanish version if the two are to be as identical as possible.

Paragraph 17

English version (2000): Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

1996 version: I.7 Physicians should abstain from engaged in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
III.3 The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

French version (2000): Un médecin ne doit entreprendre une étude que s'il estime que les risques sont correctement évalués et qu'ils peuvent être contrôlés de manière satisfaisante. Il doit être mis un terme à la recherche si les risques se révèlent l'emporter sur les bénéfiques sont apportées.

1996 version: I.7 Un médecin ne doit entreprendre un projet de recherche que s'il estime être en mesure d'en prévoir les risques potentiels. Un médecin doit arrêter l'expérience si les risques se révèlent l'emporter sur les bénéfices escomptes.
III.3 L'expérimentateur ou l'équipe de recherche doivent arrêter l'expérience si, à leur avis, sa poursuite peut être dangereuse pour le sujet.

17.1F The English version requires that physicians not participate in research projects unless 'they are confident' of the adequate assessment and management of risks. In the French version the physician 'estime' (lit. considers, estimates) that the risks are assessable and manageable.

Back translations:

(1) A physician must undertake a study only if he considers that the risks are correctly assessed and that they can be controlled satisfactorily. The research must be stopped if the risks prove to prevail over the expected benefits, or if substantial proofs of positive and beneficial results fail to be provided.

(2) Doctors must undertake a study only if they believe that the risks are correctly assessed and can be controlled in a satisfactory way. Research should be stopped if risks prove to be greater than the benefits expected or if substantial evidence of positive and beneficial results is brought.

(3) A physician must not undertake a research project unless they believe to have properly taken into consideration all the possible risks and that these risks can be controlled in an acceptable manner. Physicians should cease any investigation if there is a sign of risk on the subject or if there is conclusive proof of positive and beneficial results.

17.1F Two of the back translators render 'estime' as 'believe' and one as 'considers'. A physician who 'believes' or 'considers' would arguably seem to be in a less emphatic and more ambivalent state of mind than a physician who is 'confident'. We suggest that a closer equivalent would be 'Un médecin ne doit entreprendre une étude amoins d'avoir confiance que les risques sont correctement évalués et qu'ils peuvent être contrôlés de manière satisfaisante'.

Spanish version (2000): Los médicos deben abstenerse de participar en proyectos de investigación en seres humanos a menos de que estén seguros de que los riesgos inherentes han sido adecuadamente evaluados y de que es posible hacerles frente de manera satisfactoria. Deben suspender el experimento en marcha si observan que los riesgos que implican son más importantes que los beneficios esperados o si existen pruebas concluyentes de resultados positivos o beneficiosos.

1996 version: I.7 Los médicos deberían abstenerse de participar en ensayos clinicos con sujetos humanos a menos que estén seguros que los riesgos que estos incluyan sean realmente predecibles. Los médicos deberían suspender cualquier investigación en el momento en que los riesgos demuestren superar a los potenciales beneficios. III.3 El investigador o el equipo de investigación deben suspender la misma si opinan que la continuación del mismo puede ser perjudicial para el paciente.

17.1S In the Spanish version, the state of mind of the physician with respect to the risks and benefits is 'seguros' which literally in English is 'sure' or 'certain'.

17.2S "Physicians should cease any investigation if..." changes to "you/they should cease the experiment in running if...". The use of the pronoun is stylistic and clearly refers to physicians. There is an enhanced emphasis in the Spanish version on the "continuing" or "running" experiment, however it is difficult to argue for a significant change in meaning here although there is a translation which would render the two more similar, i.e. "Medicos deben cesar cualquiera investigacion si".

17.3S "If the risks are found to outweigh the potential benefits" (Eng.) becomes "if it observed that the implicated risks are more important than the benefits hoped for" (Sp.). Clearly the style changes considerably – but does the meaning? The addition of the word 'implicated' changes nothing – except to 'implicate the research" in responsibility for the risks – which is implied in the English version. The notion of "more important" is simply a literal way of phrasing the more metaphorical English "outweigh" (where the concept of "scales" is in the background). There is not really a change to meaning here.

17.4S "Positive AND beneficial" becomes "positive OR beneficial" (Sp.). The change in use of the Boolean operator from AND to OR is perhaps perplexing but arguably there is no change in meaning. This is because it is arguable that one of the English words "positive", "beneficial" is redundant in context. This paragraph pertains to the situation of an early stopping of an experiment because there is a clear benefit apparent with the new treatment and it would be unethical to continue to use the old treatment. It does not address the issue of early stopping because of adverse effects of the new treatment. That has already been covered. Therefore the question arises as to what is the difference between positive and beneficial in the context of the English version. How could a positive results in this context not be beneficial and vice versa. If a result is positive if and only if it is beneficial (and I argue that this is so in the context) then there is justification for using 'or' in Spanish because the end result is the same meaning. In fact, in this situation the Spanish is probably more correct because it presents 'beneficial' as an alternative way of seeing 'positive' whereas the English perhaps mistakenly conveys the notion that 'beneficial' adds something to the word 'positive'.

Back translations:

(1) Doctors must refrain from participating in research projects on human beings unless they are sure that the inherent risks have been properly assessed and that is possible to face them in a satisfactory way. The experiment must be cancelled if they observe that the implied risks are more important than the benefits expected or if conclusive evidence of positive or beneficial results exist.

(2) Doctors must abstain from participating in research projects on human beings unless they are sure that the inherent risks have been adequately evaluated and that it is possible to face them in a satisfactory manner. They must supend an experiment in process if they observe that the risks involved are more important than the expected benefits or if there is conclusive proof of positive results or benefits.

(3) Doctors can only participate in human medical research if they are sure that all the risks have been adequately evaluated and considered. Doctors

must stop any experiment if they observe that risks outweigh any possible benefits or if it becomes known that the results will be positive or beneficial.

17.1S The back translations all retain the word 'sure'. This is a very different situation from being confident. Sure or certain has a 100% notion to it whereas confident would allow for a small possibility of error. Certainty is really impossible in the context of research – because if the answers are known then why do the research? Equipoise would not exist. We suggest that a version which reads "...menos de que tengan suficiente confianza de que..." would both render the Spanish as close as possible to the English and would convey the preferred message here.

17.2S Only the 2nd of the back translations preserves the sense of an experiment in progress. The others make no such reference. There is probably no case for a change here, although the possible phrasing to make the match more exact is suggested above.

17.3S One of the back translations has spontaneously chosen the word "outweigh" with its metaphorical connotations mentioned above, while the other two do not. However, there really is no case to be made that there is any shift in meaning. There is arguably a stylistic difference. To change the English to literally match the Spanish or viceversa risks introducing 'woodenness' into the phrasing.

17.4S The back translations retain the difference observed – all use the Boolean operator 'or'. There is no reason why 'and' could not be used in the Spanish version and this slight change would make the translations more exact. There could be an argument made that a positive outcome is not always beneficial. Suppose we are testing the null hypothesis that treatment B causes no more unpleasant side effects than treatment A. The results show that treatment B indeed has a statistically significantly greater number of side effects. This could be described as a positive result (i.e. the null hypothesis would be discarded in favour of the alternative hypothesis) but it is certainly not a beneficial one. There is room for ambiguity in the use of 'or'. We suggest that either the Spanish version uses 'and' or that both it and the English version change to match the French version which only speaks of beneficial results and avoids the word 'positive' and so removes the necessity for any connecting word at all.

Paragraph 18

English version (2000): Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and

burdens to the subject. This is especially important when the human subjects are healthy volunteers.

1996 version: I.4 Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

French version (2000): Une etude ne peut être réalisée que si l'importance de l'objectif recherché prévaut sur les contraintes et les risque encourus par le sujet. C'est particulièrement le cas lorsqu'il s'agit d'un volontaire sain.

1996 version : I.4 L'expérience ne peut être tentée légitimement que si l'importance du but visé est en rapport avec le risque encouru par le sujet.

18.1F Whereas the English version spells out 'medical research involving human subjects' as the subject of the sentence, the French uses the less descriptive 'a study' as the subject of the sentence. This is stylistic only and does not change the meaning. No other particular difference between the English and French versions was found on initial analysis.

Back translations:

(1) A study can only be carried out if the importance of the aim sought prevails over the constraints and the risks incurred by the subject. This is particularly so when a healthy subject is at stake.

(2) A study can be made only if the importance of the aimed objective prevails over the risks and constraints incurred by the subject. It is especially the case when dealing with a healthy subject.

(3) A study cannot be carried out unless the importance of the objective outweighs the constraints and risks run by the subject. It is particularly the case when concerning a volunteer.

18.1F The back translations confirm the difference in subject of the sentence. Arguably the two versions would be more exactly equivalent if the subjects of the sentence were harmonised. Given the vagueness of the term 'a study', and the fact that both the English and Spanish versions use "medical research involving human subjects", we prefer the versions which brings the reader back to the overall subject of the Declaration "Medical research involving human subjects".

Spanish version (2000): La investigación médica en seres humanos sólo debe realizarse cuando la importancia de su objetivo es mayor que el riesgo inherente y

los costos para el individuo. Esto es especialmente importante cuando los seres humanos son voluntarios sanos.

1996 version: I.4 La investigación biomédica en sujetos humanos no puede ser llevada hasta el final en forma legítima a menos que la importancia del objetivo de ella misma esté en proporción al riesgo inherente para el paciente de la misma.

18.1S "The inherent risks and burdens" (Eng.) becomes "the inherent risks and costs" (Sp.). This is different from 16.1S where the Spanish version leaves out any reference beyond 'risks'. What is difficult to explain is why it is now included here. The notion of 'costs' having a financial implication is discussed in 16.1S.

Back translations:

(1) Medical research on human beings must be solely conducted when the significance of its aim is higher than both the inherent risk and the costs for the individual. This is particularly important when the human beings are healthy volunteers.

(2) Medical research on human beings must only be carried out when the importance of the objective is greater than the inherent risk and the costs to each individual. This is especially important when the human beings are healthy volunteers.

(3) Human medical research can only be undertaken when objectives outweigh any inherent risk and burden for the individual. This is especially important when participants are healthy volunteers.

18.1S One of the back translations uses 'burden' as the translation of 'costos'. The others remain with the narrower notion of 'costs'. One possibility would be to use the Spanish 'cargas' to reflect more closely the notion of burden.

Paragraph 19

English version (2000): Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefits from the results of the research.

1996 version: No equivalent.

French version (2000): Une recherche médicale sur des êtres humains n'est légitime que si les populations au sein desquelles elle est menée ont des chances réelles de béneficier des résultats obtenus.

1996 version : No equivalent.

19.1F The phrase 'reasonable likelihood' in English appears in the French version as 'chances réelles'. This we argue represents a significant shift in meaning. A chance may be 'real' yet very small. A one in a million chance of winning the lottery is a 'real' chance in the sense that a chance exists, i.e., it is not impossible, but may not represent a reasonable justification for buying a ticket.

Back translations:

(1) Medical research on human beings is rightful only if the populations amongst which it is carried out have real chances of benefiting from the results obtained.

(2) A medical research on human beings is legitimate only if the populations among which it is carried out have realistic changes to benefit from the results obtained.

(3) Medical research involving humans are not legitimate unless the societies to which the human subjects belong can eventually benefit from the results of the research.

19.1F The 1st back translation simply uses 'real'. The 2nd interestingly uses 'realistic' which, arguably, broadens the meaning toward the notion of 'reasonable'. In the final back translation the translator has avoided the issue by changing the sentence structure. While the back translation results are unclear, we argue that there is no reason that the French version could not 'chances raisonnables'.

Spanish version (2000): La investigación médica sólo se justifica si existen posibilidades razonables de que la población, sobre la que la investigación se realiza, podrá beneficiarse de sus resultados.

1996 version: No equivalent.

No unnecessary differences were detected between the English and the Spanish versions on initial analysis.

Back translations:

(1) Medical research is only justified when a reasonable likelihood exists that the population, into which the research is conducted, will be able to benefit from the results.

(2) Medical research is only justified if there is a reasonable possibility that the population, on which the research is carried out, will be able to benefit from the results.

(3) Medical research is only appropriate if there are reasonable chances that the population being researched will benefit from the results.

The back translations did not suggest that any differences had been missed on initial analysis.

Paragraph 20

English version (2000): The subjects must be volunteers and informed participants in the research project.

1996 version: III.2 The subjects should be volunteers – either healthy persons or patients for whom the experimental design is not related to the patient's illness.

French version (2000): Les sujets se prêtant à des recherches médicales doivent être des volontaires informés des modalités de leur participation au projet de recherche.

1996 version : III.2 Les sujets doivent être des volontaires en bonne santé ou des malades atteints d'une affection étrangère à l'étude.

20.1F The French version adds an adjectival clause referring to 'the subjects taking part in medical research' whereas the English has only 'the subjects'. This difference is unnecessary but does not alter the meaning.

20.2F The French version is more explicative than the English of what the participants need to be informed about, adding the word 'modalités', literally the 'terms of' or 'practical details of' their participation in research. Again it is difficult to argue that the meaning changes but it is arguable that the difference is unnecessary.

Back translations:

(1) The subjects who lend themselves to medical research must be volunteers informed of the details of their participation to the research project.

(2) Subjects participating in medical research have to be volunteers who are informed of the modalities of their participation in the research project.

(3) The research subjects who lend themselves to medical research must be volunteers informed on the modalities of their participation in the research project.

20.1F The back translations perpetuate this difference. To make the versions as exact as possible, the English should either incorporate the qualifying clause or the French should remove it. Since the first paragraph of the Declaration as well as its heading defines what 'the subjects' would be subjects of (i.e. medical research), a good argument could be made for being parsimonious with words and opting for the shorter English version.

20.2F The English is arguably very vague in describing subjects as 'informed'. An argument could be made that this simply means they are 'educated' or have good general knowledge! The French does a better job of articulating briefly in what sense subjects are to be 'informed' and we suggest a change in the English here to something along the lines of back translation 1 (above) but without the additional referred to in 20.1F and with the appropriate preposition, i.e. 'the subjects must be volunteers informed of the details of their participation in the research project'.

Spanish version (2000): Para tomar parte en un proyecto de investigación, los individuos deben ser participantes voluntarios e informados.

1996 version: III.2 Los pacientes deberán ser voluntarios : tanto personas sanas como pacientes cuya enfermedad no esté relacionada con el diseño experimental.

20.1S The Spanish changes the structure of the sentence but it is arguable that this is necessitated for the sentence to read grammatically correctly in Spanish. There is no obvious Spanish alternative which would render it closer to the English version.

Back translations:

(1) To take part in a research project, the individuals must be voluntary and informed participants.

(2) To take part in a research project, the individuals must be voluntary and informed participants.

(3) Individuals who take part in any research experiment must be well-informed volunteers.

20.1S Given that the objective of the WMA is to have the 3 versions as identical as possible, there is a case for changing the English to something like 'To take part in a research project, subjects must be volunteers and they must be informed of the details of what their participation involves'. If this were done, there would also need

to be concomitant changes to the Spanish to bring it fully in line with the French version and the changed English version.

Paragraph 21

English version (2000): The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

1996 version: I.6 The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

French version (2000): Le droit du sujet à la protection de son intégrité doit toujours être prises pour respecter la vie privée du sujet, la confidentialité des données le concernent et limiter les répercussions de l'étude sur son équilibre physique et psychologique.

1996 version: I.6 Le droit du sujet à sauvegarder son intégrité et sa vie privée doit toujours être respecté. Toutes précautions doivent être prises pour réduire les répercussions de l'étude sur l'intégrité physique et mentale du sujet, ou sur sa personnalité.

21.1F In English 'mental integrity and ... personality' becomes simply 'équilibre ... psychologique' in French.

Back translations:

(1) The right of the subject to the protection of his/her integrity must always be respected. All precautions must be taken to respect the private life of the subject, the confidentiality of the data relating to him/her and to limit the consequences of the study on his/her physical and psychological equilibrium.

(2) The right of the subject to the protection of his integrity must always be respected. All precautions must be taken to respect the privacy of the subject, the confidentiality of the data concerning him, and limit the repercussions of the study on his physical and psychological balance.

(3) The rights of the research subject's integrity must always be respected. Every precaution must be taken to respect the privacy of the subject, the confidentiality of the data concerning the subject, and to limit the repercussions of the study on his or her physical and psychological being.

21.1F The back translations all preserve the observed difference between the French and English versions. It must be asked: would anything be lost by changing the English version to "minimise the impact of the study on the subject's physical and psychological integrity"? This change would certainly make the two versions more exact translations of one another.

Spanish version (2000): Siempre debe respetarse el derecho de los participantes en la investigación a proteger su integridad. Deben tomarse toda clase de precauciones para resguardar la intimidad de los individuos, la confidencialidad de la información del paciente y para reducir al mínimo las consecuencias de la investigación sobre su integridad física y mental y su personalidad.

1996 version: I.6 Debera respetarse siempre el derecho del paciente de salvaguardar su integridad. Se tomarán todas las precauciones para respetar la privacidad del paciente y para minimizar el impacto del estudio en la integridad física y mental del paciente, así como en la personalidad del mismo.

21.1S "Respect" (Eng.) becomes "safeguard" (Sp.). The semantic shift is slight and arguably unimportant. However, 'respect' reflects an attitude (which should then dictate action) whereas 'safeguard' has more direct connotations of action.

21.2S "To minimise the impact" (Eng.) is effectively the same meaning as "To minimise the consequences" (Sp.). The Spanish version, as in 17.3S is more literal. The English version has recourse to a metaphorical notion of "impact" (i.e. something hitting something) but in context creates the same meaning as the literal word "consequences" would. However, it could be argued that either version could change to be a more exact translation of one another.

Back translations:

(1) The right of the research participants to protect their integrity must always be respected. All types of precautions must be taken to safeguard the individuals' privacy, the patient's information confidentiality and to minimise the consequences of the research over their physical and mental integrity and their personality.

(2) The rights of the participants in the research must always be respected to protect its integrity. Every precaution should be taken to protect the privacy of the individuals, the confidentiality of patient information and

to reduce to the minimum the consequences of the research on his physical and mental integrity and his personality.

(3) Research participants must always have the right to protect their integrity. Precautions must be taken to preserve any confidential information and patient privacy. Any consequences for patients' personality, physical or mental integrity must be reduced to the minimum.

21.1S The Spanish version 'safeguard' is rendered as 'safeguard', 'protect', and 'preserve' in the 3 back translations. However, all of these have more of an 'action' orientation than 'respect'. Since the paragraph calls for 'precaution[s] to be taken', we argue that the Spanish has got it right and the English version would both become closer to the Spanish version and be better worded if 'every precaution must be taken to safeguard the privacy of the subject'.

21.2S The 3 back translations preserve 'consequences'. Either the Spanish version or the English version could easily change here to become more exact translations of one another. Given the French version is 'repercussions' (which is back-translated once as 'consequences' and twice as 'repercussions'), perhaps the word 'repercussions' is an appropriate choice.

Paragraph 22

English version (2000): In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

1996 version: I.9 In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

French version (2000): Lors de toute étude, la personne se prêtant à la recherche doit être informée de manière appropriée des objectifs, méthodes, financement, conflits d'intérêts éventuels, appartenance de l'investigateur à une ou des institutions, bénéfices attendus ainsi que des risques potentials de l'étude et des contraintes qui pourraient en résulter pour elle. Le sujet doit être informé qu'il a la faculté de ne pas participer à l'étude et qu'il est libre de revenir à tout moment sur son consentemente sans crainte de préjudice. Après s'être assuré de la bonne compréhension par le sujet de l'information donnée, le médecin doit obtenir son consentement libre et éclairé, de préférence par écrit. Lorsque le consentement ne peut être obtenu sous forme écrite, la procédure de recueil doit être formellement explicitée et reposer sur l'intervention de témoins.

1996 version : I.9 Lors de toute recherche sur l'homme, le sujet éventuel sera informé de manière adéquate des objectifs, méthodes, bénéfices escomptés ainsi que des risques potentiels de l'étude et des désagréments qui pourraient en résulter pour lui. Il (elle) devra être informée qu'il (elle) a le privilège de ne pas participer à l'expérience et qu'il (elle) est libre de revenir sur son consentement à tout moment. Le médecin devra obtenir le consentement libre et éclairé du sujet, de préférence par écrit.

22.1F The English version uses 'discomforts' where the French uses 'contraintes'. However, there is no easy way of directly translating 'discomforts' into French – 'manque d'aise' is perhaps a possibility.

22.2F In English non-written informed consent must be 'formally documented and witnessed' whereas in French it 'doit être formellement explicitée et reposer sur l'intervention de témoins'.

Back translations:

(1) During all studies, the person lending him/herself to the research must be informed appropriately of the aims, methods, financing, possible conflicts of interest, membership of the investigator to one or several institutions, expected benefits, as well as of the potential risks of the study and the possible resulting constraints for him/her. The subject must be informed that he/she has the possibility not to take part in the study and that he/she is free to go back on his/her consent at any time without fear of prejudice. After he/she is sure that he/she well understands the information given, the physician must obtain his/her free and enlightened consent, preferably in writing. When the consent cannot be obtained in a written form, the recording (of consent) procedure must be formally explained and involve the use of witnesses.

(2) During every study the person who participates in the research must be appropriately informed of the objectives, methods, funding, possible conflicts of interests, membership of the investigator to any institution, expected benefits as well as the potential risks of the study and the constraints that might result for him. The subject must be informed that he has the right of not participating in the study and that he is free to reconsider his consent anytime without fear of prejudice. After he has made sure that the information given to the subject has been fully understood, the doctor must obtain his free and enlightened consent, preferably written. When consent cannot be obtained on a written document, the procedure of recording must be formally explained and rest on the intervention of witnesses.

(3) In any study, the person lending themselves to the research must be properly informed of the objectives, methods, funding, eventual conflicts of interest, affiliations of the Investigator Researcher to one or any institutions, of the benefits sought out as well as the potential risks of the study and the constraints that may result on the human subject. The subject must be informed that he or she has the right to no longer participate to the study and that they are free to withdraw their consent without fear of prejudice. After having been assured of the patient's comprehension on the information given, the physician must obtain a free and clear written consent from the subject. When consent cannot be obtained in written form, the procedure for consent must be formally explicit and include the presence of witnesses.

22.1F All 3 back-translations preserve the word 'constraints'. This would not be the chosen word in English for what is being communicated. This is probably an example where there really is no way of finding an exact translation between the two without circumlocution.

22.2F The differences between the English 'formally documented' and French 'formally explained' or 'explicit' is retained in the back translations. An option to make the two more exact translations of one another is to use 'documentée' in the French version.

Spanish version (2000): En toda investigación en seres humanos, cada individuo potencial debe recibir información adecuada acerca de los objetivos, métodos, fuentes de financiamiento, posibles conflictos de intereses, afiliaciones institucionales del investigador, beneficios calculados, riesgos previsibles e incomodidades derivadas del experimento. La persona debe ser informada del derecho de participar o no en la investigación y de retirar su consentimiento en cualquier momento, sin exponerse a represalias. Después de asegurarse de que el

individuo ha comprendido la información, el médico debe obtener entonces, preferiblemente por escrito, el
consentimiento informado y voluntario de la persona. Si el consentimiento no se puede obtener por escrito, el proceso para lograrlo debe ser documentado y atestiguado formalmente.

1996 version: En cualquier investigación llevada a cabo en sujetos humanos, cada paciente potencialmente participante deberá ser informado adecuadamente sobre los potenciales riesgos y beneficios así como también la incomodidad que puede presentarse. También deberá informásele que el mismo es totalmente libre de abstenerse de la participación en el estudio, así como también de retirar su consentimiento en cualquier momento. El médico debería obtener luego el libre consentimiento del paciente para participar en el estudio, preferentemente por escrito.

22.1S Freely given informed consent" (Eng.) becomes "informed and voluntary consent" (Sp.). This is a stylistic difference which, although preserved in the back-translation, does not change the meaning. "Freely-given" and "voluntary" in this context are synonymous.

22.2S Spanish version in this case seem to express more effectively what the English declaration is trying to say regarding fromally documenting and witnessing 'non-written' consent, by stating "If the consent cannot be obtained in writing, the process carried out to achieve it should be formally documented and witnessed." This is and example of a stylistic change made actually adding to the original version.

Back translations:

(1) In every research on human beings, each potential individual must receive proper information about the aims, methods, sources of funding, possible conflict of interests, researcher's membership, estimated benefits, foreseeable risks and inconveniences derived from the experiment. The person must be informed about the right to accept or refuse participation in the research and to the withdrawal of their consent at any moment, without exposing themselves to reprisals. After ensuring that the individual has understood the information, the doctor must then obtain, preferably in writing, the individual's informed and voluntary consent. If the consent cannot be obtained in writing, the process to obtain it must be both documented and formally witnessed.

(2) In all research on human beings, each potential individual must receive adequate information on the objectives, methods, sources of finance, possible conflicts of interest, institutional affiliations of the researchers, calculated benefit, foreseeable risks and inconvenience resulting from the

experiment. The person must be informed of the right to participate or not in the research and to withdraw his consent at any moment, without laying himself open to reprisals. After ensuring that each individual has understood the information, the doctor must obtain, preferably in writing, the informed and voluntary consent of the person. If it is not possible to obtain the consent in writing, the process to obtain it must be documented and formally witnessed.

(3) In any human research, every potential participant must be properly informed about objectives, methods, financial sources, any possible conflict of interests, researchers' institutional affiliations, calculated benefits, foreseeable risks and any inconvenience associated with the experiment. The potential participant must be informed of the right to participate or not in the investigation and to withdraw his or her consent at any moment without reprisal. Doctors must request, preferably in writing, the informed and voluntary consent, only after they are sure that a patient has understood the information. If the consent is not possible in writing, the process to achieve it must be documented with a witness.

22.1S The back translations preserve the difference between the Spanish and the English, i.e. 'informed and voluntary' (Sp.) compared with 'freely-given informed' (Eng.). However, these phrases seem to be so synonymous with one another that a case for change is weak and in this case the two versions can be considered more-or-less exact translations of one another.

22.2S The back translations preserve the difference although interestingly the adjective 'formally' is seen to apply to 'witnessed' rather than to both 'documented and witness'. Here the French and Spanish versions also differ with the French version seeming to place 'formally' with 'documented'. Our suggestion is to change the English from 'the non-written consent must be formally documented and witnessed' to something like 'If the consent cannot be obtained in writing, the process to obtain it must be both documented and formally witnessed' thus clarifying the requirement of this paragraph. A way needs to be found to harmonise the application of the adjective between the French and Spanish versions.

Paragraph 23

English version (2000): When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the

informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

1996 version: I.10 When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

French version (2000): Lorsqu'il sollicite le consentement éclairé d'une personne à un projet de recherche, l'investigateur doit être particulièrement prudent si le sujet se trouve vis-à-vis de lui dans une situation de dépendance ou est exposé à donner son consentement sous une forme de contrainte. Il est alors souhaitable que le consentement soit sollicité par un médecin bien informé de l'étude mais n'y prenant pas part et non concerné par la relation sujet-investigateur.

1996 version : I.10 Lorsqu'il sollicite le consentement éclairé du sujet au projet de recherche, le médecin devra prendre des précautions particulières si le sujet se trouve vis-à-vis de lui dans une situation de dépendance ou doit donner son consentement sous la contrainte. Dans ce cas, il serait préférable que le consentement soit sollicité par un médecin non engagé dan l'experiénce en cause et qui soit complètement étranger à la relation médecin-sujet.

23.1F In a situation where there is any suggestion of dependence or consent under duress the English version states that consent must be obtained by "a well-informed physician who is ... completely independent of the relationship". In French there is no equivalent of the adjective "completely".

23.2F The English version uses the demonstrative pronoun "In that case" to begin the second sentence whereas French uses an ordinary pronoun "Il est alors..."

Back translations:

(1) When the investigator requests the enlightened consent of a person for a research project, he/she must be particularly cautious if the subject finds him/herself in a situation of dependence towards the investigator, or if the subject may give his/her consent under some form of constraint. In such cases it is desirable that the consent is sought by a physician well-informed of the study but not taking part in it, and with no connection to the subject-investigator relation.

(2) When soliciting enlightened consent to a research project from somebody, the investigator must be especially cautious if the subject finds himself in a situation of dependence on him or if he is exposed to give his

consent under a form of constraint. It is then desirable that consent be asked by a doctor who is well informed of the study but does not take part in it, and is not concerned by the relation between the subject and the investigator.

(3) When a research investigator seeks informed consent from an individual for a research project, they must be particularly careful if the research subject is a dependent or is exposed to give his consent under duress. It is therefore suggested that the consent be solicited by a physician well-informed on the study but not taking part and not concerned by the relationship between the subject and the researcher.

23.1F The absence of the adjective is, as would be expected, confirmed by the back translations. Whether there is a difference in meaning hinges on whether "independent" and "completely independent" mean the same thing. It is arguable that nothing is lost if the English version drops "completely" and both parsimony and a greater equivalence with the French version are obtained.

23.2F The difference between "in that case" and "it is then/therefore" is really stylistic and probably not worth considering any changes here.

Not detected on initial analysis was another difference which the back translations reveal. The French version specifies that the other physician must be "well informed" with respect to the study whereas the English version simply says "well-informed". Here, the French version is more precise – it is the knowledge of the study which is relevant – and the English version could be improved and brought closer to the French version by a corresponding change.

Spanish version (2000): Al obtener el consentimiento informado para el proyecto de investigación, el médico debe poner especial cuidado cuando el individuo está vinculado con él por una relación de dependencia o si consiente bajo presión. En un caso así, el consentimiento informado debe ser obtenido por un médico bien informado que no participe en la investigación y que nada tenga que ver con aquella relación.

1996 version: I.10 Cuando se obtenga el consentimiento el médico deberá ser particularmente cauteloso si el paciente se encuentra en una relación de dependencia respecto a él o que pueda consentir bajo presión. En este caso el consentimiento deberá ser obtenido por un médico que no esté a cargo de la investigación y que sea completamente independiente del paciente.

No specific differences were detected on initial analysis between the English and Spanish versions.

Back translations:

(1) When obtaining the informed consent for the research project, the doctor must take special care when the individual is linked to him/her through a relation of dependency and gives their consent under pressure. In a case like this, the informed consent must be obtained by a well-informed doctor who does not participate in the research and is not linked at all with the relationship aforementioned.

(2) To obtain informed consent for the research project, the doctor must take special care when the individual is linked to him in a dependent relationship or if he consents under pressure. In such a case, the informed consent must be obtained by a well-informed doctor who is not participating in the research and who could not be seen to have such a relationship.

(3) Doctors must be very careful when the patient has a dependent relationship with them or where the patient may give consent under pressure for the research. If this is the case, the informed consent must be taken by a well-informed doctor who does not participate in the research and who has nothing to do with that relationship between researcher and patient.

No particular differences are suggested by the back translations that would warrant a change to either the English or Spanish version. There is no overt adjective completely but the sense of the Spanish which comes through in at least two of the back translations (e.g. "is not linked at all", "has nothing to do with") seems to have such a connotation.

Paragraph 24

English version (2000): For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent form the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

1996 version: I.11a In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or

when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

French version (2000): Lorsque le sujet pressenti est juridiquement incapable, physiquement ou mentalement hors d'etat de donner son consentement ou lorsqu'il s'agit d'un sujet mineur, l'investigateur doit obtenir le consentement éclairé du représentant légal en conformité avec le droit en vigueur. Ces personnes ne peuvent être inclues dans une étude que si celle-ci est indispensable à l'amélioration de la santé de la population à laquelle elles appartiennent et ne peut être réalisée sur des personnes aptes à donner un consentement.

1996 version : I.11a En cas d'incapacité légale et notamment s'il s'agit d'un mineur, le consentement devra être sollicité auprès du représentant légal, compte tenu des législations nationales. Au cas où une incapacité physique ou mentale rend impossible l'obtention d'un consentement éclairé, l'autorisation des proches parents responsable remplace, sous la même réserve, celle du sujet.

24.1F In English, the subject of the 2nd sentence is "These groups" whereas in French it is "Ces personnes" (lit. "These people"/ "these persons").

Back translations:

(1) When the prospective subject is a legally incapable person, either physically or mentally unable to give his/her consent, or when the subject is under-aged, the investigator must obtain the enlightened consent of the legal representative of this person, in accordance with the laws in force. These people can be included in a study only if it is essential to the improvement of the health of the population to which they belong, and if the study cannot be carried out on people able to give their consent.

(2) When the prospective subject is in juridical terms incapable, when he is physically or mentally unfit to give his consent, or when dealing with a subject who is a minor, the investigator must obtain the enlightened consent of the legal representative in accordance with the law in force. These persons can be included in a study only if this study is indispensable to the improvement of the health of the population to which they belong and cannot be made on persons who are able to give consent.

(3) When the research subject is legally incompetent, physically or mentally incapable to give their consent, or when dealing with a minor, the investigator researcher must obtain the clear consent of the legal representative in accordance with the applicable law. These subjects cannot be included in a study unless the research is vital to the betterment

of the health of the population to which they belong, and cannot be carried out on persons apt to give consent.

24.1F The back translations preserve the difference in the subject of the sentence. Technically speaking, the French is more correct than the English semantically because it is the "person" (i.e. a person from the group referred to in the English version). It is a minor technicality and there is no sense in which the meaning is unclear but the English version would be improved by a change to "These people" or "Such people".

Spanish version (2000): 24. Cuando la persona sea legalmente incapaz, o inhábil física o mentalmente de otorgar consentimiento, o menor de edad, el investigador debe obtener el consentimiento informado del representante legal y de acuerdo con la ley vigente. Estos grupos no deben ser incluidos en la investigación a menos que ésta sea necesaria para promover la salud de la población representada y esta investigación no pueda realizarse en personas legalmente capaces.

1996 version: I.11a En case de incompetencia legal, el consentimiento será obtenido de un tutor legal de acuerdo a las leyes locales. En case de discapacidad mental o de ser menor de edad, el permiso obtendio por la persona responsable reemplaza relativamente al del paciente de acuerdo a la legislación local.

24.1S The English version has "legally incompetent minor" whereas the Spanish uses "Underage / minor" losing any direct reference to legality. There is no change to the meaning of the paragraph introduced by this change as what else can "underage" mean besides legally underage. Interestingly the words "minor child" used in Paragraph 25 in the English version is rendered in Spanish in exactly the same manner.

Back translations:

(1) When the person is legally incapable, or physically or mentally ineligible to give his/her consent, or under age, the researcher must obtain the informed consent from a legal representative and in compliance with the current legislation in force. These groups must not be included in the research unless this is necessary to promote the health of the represented population and this research cannot be conducted on people legally able.

(2) When a personally is legally incapable, or physically or mentally unfit to give consent, or a minor, the researcher must obtain the informed consent of the legal representative and in accordance with prevailing law. These groups must not be included in research unless this is necessary to promote the health of the population represented and this research cannot be carried out on legally capable persons.

(3) When a patient is legally incompetent or unable physically or mentally to give consent, such as a minor, the researcher must obtain the informed consent from his or her legal agent, in accordance with the law. These groups of people must not be included in research unless such research is necessary to promote the health of the population they represent and only where this research could not be done with people legally competent.

24.1S The back translations also simply refer to 'minor' or 'under age'. This parallels the French version as well although this difference was not detected in the initial analysis. The question of whether "legally incompetent minor" means anything more than "minor" will determine whether there is any meaning difference. It does not seem that there is and the English version could simply say 'minor' as do the others.

We also note that the Spanish version, like the English, speaks of "groups" in the 2nd sentence (and interestingly one back translation has spontaneously rendered this "These groups of people"). For the reasons described above, we suggest this is changed to parallel the French version, i.e. "These people".

Paragraph 25

English version (2000): When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

1996 version: I.11b Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

French version (2000): Lorsque le sujet, bien que juridiquement incapable (un mineur par example), est cependant en mesure d'exprimer son accord à la participation à l'étude, l'investigateur doit obtenir que cet accord accompagne celui du reprèsentant légal.

1996 version : I.11b Lorsque l'enfant mineur est capable de donner son consentement, celui-ci devra être obtenu en plus du consentement de ses responsables légaux.

25.1F The English version speaks of requiring 'assent' of a minor child capable of giving such assent, whereas the French version speaks of 'accord'.

Back translations:

(1) When the subject, even though legally incapable (under-aged for instance), is however able to express his/her agreement to participating in the study, the investigator must obtain this agreement alongside that of the legal representative.

(2) When the subject, though in juridical terms incapable (for example a minor), is however able to express agreement to participation in the study, the investigator must obtain this agreement being in accordance with the agreement of the legal representative.

(3) When a subject deemed legally incompetent as in the case of a minor is however in the right to express their agreement to the participation of the study, the investigator must obtain an agreement accompanied by a legal representative.

25.1F Notwithstanding the fact that the back-translations seem to have confused slightly the translation back into English the final phrase of Paragraph 25, they have all used the word 'agreement' to translate 'accord'. In French it is possible that a closer synonym to 'assent' would be 'assentiment'. There is no meaning change provided that 'assent' and 'agreement' are considered completely synonymous. Perhaps, however, it would be preferable to either change the English to 'agreement' or the French to 'assentiment'.

Spanish version (2000): 25. Si una persona considerada incompetente por la ley, como es el caso de un menor de edad, es capaz de dar su asentimiento a participar o no en la investigación, el investigador debe obtenerlo, además del consentimiento del representante legal.

1996 version: I.11b Siempre que un menor esté capacitado para dar su consentimiento, el mismo debe ser obtenido en forma adicional al consentimiento del padre y/o tutor legal.

There were no specific differences identified on initial analysis.

Back translations:

(1) If a person qualified as ineligible by law, as in the case of an under age, is able to give their approval to participating or otherwise in the research, the researcher must obtain it, as well as the consent of the legal representative.

(2) If a person considered incompetent by law, as is the case with a minor, is capable of giving his assent to participate or not in the research, the researcher must obtain it, as well as the consent of the legal representative.

(3) If a person considered incompetent by law, such as a minor, can give assent to participate in the research, doctors must obtain his or her assent as well as the consent of his or her legal agent.

No particular differences were suggested by the back-translations. Interestingly, one translator rendered 'asentimiento' as 'approval'; the others as 'assent'. Therefore if the English were changed to 'agreement', consideration would need to be given to changing the Spanish as well.

Paragraph 26

English version (2000): Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

1996 version: No equivalent.

French version (2000): La recherche sur des personnes dont il est impossible d'obtenir le consentement éclairé, même sous forme de procuration ou d'expression préalable d'un accord, ne doit être conduite que si l'état physique ou mental qui fait obstacle à l'obtention de ce consentement est une des caractéristiques requises des sujets à inclure dans l'étude. Les raisons spécifiques d'inclure des sujets dans une étude en dépit de leur incapacité à donner un consentement éclairé doivent être exposées dans le protocole qui sera soumis au comité pour examen et approbation. Le protocole doit également préciser que le consentement du sujet ou de son représentant légal à maintenir sa participation à l'étude doit être obtenu le plus rapidement possible.

1996 version : No equivalent.

26.1F The French version in the 3rd sentence requires 'Le protocole doit également préciser' (lit. 'The protocol should specify as well') whereas the English version

simply says 'The protocol should state'). The statement in French appears to carry more intensity than the rather bland requirement in the English version.

26.2F There is a change from the positively stated (with qualifying clause) English version ('should only be done if') to the French version which uses a negative statement with an exceptive clause 'ne doit être conduite que si' (lit. 'should not be done unless').

Back translations:

(1) Research on people from whom it is impossible to obtain an enlightened consent, even by proxy or by prior expression of an agreement, must only be conducted if the physical or mental state which hinders the obtaining of this consent is one of the required characteristics of the subjects who are to be included in the sutyd. The specific reasons for including some subjects in a study in spite of their inability to give an enlightened consent must be explained in the protocol which will be submitted to the committee for examination and approval. The protocol must also specify that the consent of the subject or that of his/her legal representative to maintain his/her participation in the study must be obtained as quickly as possible.

(2) Research on persons whom obtaining the enlightened consent, even under a proxy form or by expressing a prior agreement, is impossible, must be carried out only if the physical or mental health preventing the obtaining of this consent is one of the characteristics required from the subjects to be including in the study. The specific reasons for including subjects in a study in spite of their incapacity to give enlightened consent must be detailed in the protocol that will be submitted to the committee for examination and approval. The protocol must also stipulate that the consent of the subject or his legal representative to maintain his participation in the study should be obtained as quickly as possible.

(3) Research on persons from whom it is impossible to obtain clear consent, even in the form of proxy or advance consent, must not be carried out unless the physical or mental condition that hinders the consent is a required characteristic of the subject to be included in the study. The specific reasons to include these subjects in a study despite their incapacity to give their consent must be stated in the protocol that will be submitted to the committee for examination and approval. The protocol must equally specify that the consent of the subject or of the subject's legal representative for the study must be obtained as soon as possible.

26.1F The intensification persists in the back-translations from the French. We suggest that a change in the English version to match more closely the French version would represent an improvement to the English version.

26.2F Here the difference in structure disappears in two of the back-translations. Clearly the notions of 'should only be done if' and 'should not be done unless' are interchangeable in the minds of the translators. In the light of this it is difficult to make the case for any change.

Spanish version (2000): 26. La investigación en individuos de los que no se puede obtener consentimiento, incluso por representante o con anterioridad, se debe realizar sólo si la condición física/mental que impide obtener el consentimiento informado es una característica necesaria de la población investigada. Las razones específicas por las que se utilizan participantes en la investigación que no pueden otorgar su consentimiento informado deben ser estipuladas en el protocolo experimental que se presenta para consideración y aprobación del comité de evaluación. El protocolo debe establecer que el consentimiento para mantenerse en la investigación debe obtenerse a la brevedad posible del individuo o de un representante legal.

1996 version: No equivalent.

No differences of concern were identified in the initial comparison of the English with the Spanish version.

Back translations:

(1) Research on individuals whose consent can not be obtained, even by their representative or in advance, must be conducted solely if the mental/physical condition that prevents obtaining the informed consent is a necessary feature of the researched population. The specific reasons why participants can not give their consent are used in the research must be set out in the experimental protocol that is submitted for consideration and approval to the assessment committee. The protocol must establish that the consent to be kept in the research must be obtained as soon as possible from the individual or their legal representative.

(2) Research on individuals from whom consent cannot be obtained, including through a representative or in advance, must be undertaken only if the physical/mental condition that prevents the obtaining of informed consent is a necessary characteristic of the population being studied. The specific reasons for using participants in the research who cannot give their informed consent must be stipulated in the experimental protocol that is presented for the consideration and approval of the evaluation committee. The protocol must establish that the consent to participate in

the research must be obtained in the shortest possible time from the individual or legal representative.

(3) When consent cannot be given prior to the research, even from a legal agent, then this must be only done if the physical/mental conditions, which prevent the consent are a necessary attribute of the population under research. The research protocol presented for consideration and approval to the committee must include the specific reasons why people that cannot give their informed consent participate in the research. The protocol must stipulate that consent to continue in the research must be obtained from the patient or his legal agent as soon as possible.

The back translations do not give rise to any additional concerns. If it were considered that the English version should be intensified with respect to the beginning of the 3rd sentence, then consideration would need to be given to whether the verb 'establecer' (twice translated as 'establish' and once as 'stipulate') matched sufficiently the intended intensity or whether there exists a better word to use here.

Paragraph 27

English version (2000): Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

1996 version: I.8 In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

French version (2000): Les auteurs et les éditeurs de publications scientifiques ont des obligations d'ordre éthique. Lors de la publication des résultats d'une étude, les investigateurs doivent veiller à l'exactitude des résultats. Les résultats négatifs aussi bien que les résultats positifs doivent être publiés ou rendus accessibles. Le financement, l'appartenance à une ou des institutions et les éventuels conflits d'intérêt doivent être exposés dans les publications. Le compte-rendu d'une étude non-conforme aux principes énoncés dans cette déclaration ne doit pas être accepté pour publication.

1996 version : I.8 Lors de la publication des résultats de la recherche, le médecin doit veiller à ce qu'il ne soit pas porté atteinte à l'exactitude des résultats. Des rapports sur une expérimentation non conforme aux principes énoncés dans cette déclaration ne devront pas être publiés.

27.1F The English version addresses 'authors and publishers' whereas the French version addresses 'les auteurs et les éditeurs de publications scientifiques'). The word 'éditeur' in French is generally means 'publisher' (though it can mean 'editor') and it is the French word 'redacteur' which more closely resembles the English 'editor'. (This kind of occurrence in language is often labelled a 'false friend' to students of language). However, the difference in the two versions consists in the specification in the French version of 'éditeurs de publications scientifiques' which does not appear in the English version.

27.2F There may be a slight difference in the requirement in English 'obliged to' (preserve the accuracy of the results) and the French 'doivent veiller' (lit. 'should watch over').

27.3F In English 'negative as well as positive results should be published or otherwise publicly available'. The French version renders 'publicly available' as 'accessible'. This would seem to mean two different things.

Back translations:

(1) The authors and publishers of scientific publications have ethical obligations. When the results of a study are published, the investigators must see to the accuracy of the results. The negative results, as well as the positive ones, must be published or made accessible. The financing, the membership to one or several institutions and the possible conflicts of interest must be explained in the publications. The account of a study which does not comply with the principles stated in this declaration must not be accepted for publishing.

(2) Authors and editors of scientific publications have obligations of ethical ethical nature. When publishing results of a study, the investigators must see to the exactitude of the results. Negative results as well as positive ones have to be published or made accessible. Funding, membership of any institution and possible conflicts of interests must be detailed in the publications. The account of a study that is not in conformity with the principles laid down in this declaration must not be accepted for publication.

(3) Both authors and publishers of scientific journals have ethical obligations. In publication of the results of a study, the investigators must strive to

maintain the accuracy of the results. Negative results as well as positive ones must be published or rendered accessible. Funding, affiliation to one or more institutions and eventual conflicts of interest must be stated in the publications. Reports of a study that do not conform to the stated principles in the declaration must not be accepted for publication.

27.1F The inclusion of 'of scientific journals' is validated in all back-translations. There is clearly a difference between the two versions. The English version could be construed to cover all authors and publishers (when they are publishing work relating to medical research involving human subjects, which is the aegis of the entire Declaration). The French version narrows the focus onto 'scientific publications'. What about medical journalism? Is there an accuracy obligation there as well? Our preference is for the broad coverage of the English version. However, an objection could be raised that this is simply too 'pie in the sky'. This is a complex question and full consideration of it is beyond the scope of a straightforward comparison.

27.2F Two back-translations render 'doivent veiller' as 'see to' and one as 'strive to maintain'. The actual meaning in practice would be substantially the same. It could be argued that a more precise equivalent could be found but this is probably a trivial point.

27.3F All 3 back-translations preserve 'accessible'. This seems a significant difference in meaning from 'publicly available', a phrase which answers the question 'accessible to whom'. Therefore we would recommend a change in the French version to 'rendus disponibles'.

Spanish version (2000): 27. Tanto los autores como los editores tienen obligaciones éticas. Al publicar los resultados de su investigación, el investigador está obligado a mantener la exactitud de los datos y resultados. Se deben publicar tanto los resultados negativos como los positivos o de lo contrario deben estar a la disposición del público. En la publicación se debe citar la fuente de financiamiento, afiliaciones institucionales y cualquier posible conflicto de intereses. Los informes sobre investigaciones que no se ciñan a los principios descritos en esta Declaración no deben ser aceptados para su publicación.

1996 version: I.8 El medico está obligado a mantener la consistencia de los resultados en sus publicaciones. Los reportes de experimentaciones que no estén acordes con los principios aquí delineados no deberían ser aceptados para su publicación.

27.1S 'The investigators' (plural) in English becomes singular in Spanish, i.e., 'El investigador'.

27.2S Whereas the English refers to an obligation to preserve the accuracy of results, the Spanish adds to this requiring 'la exactitud de los datos y resultados' ('the accuracy of the data and results).

27.3S In Spanish the requirement regarding disclosure of conflicts of interests and institutional affiliations is that they 'should be cited' (in Spanish 'se debe citar') whereas in English they 'should be declared'. The English version has stronger connotations of revelation than the Spanish which is arguably a blander way of stating this.

Back translations:

(1) Both authors and publishers have ethical obligations. When publishing his/her research results, the researcher is obliged to be accurate regarding the data and results. Both the negative and positive results must be published or otherwise they must be made available to the public. The source of funding, membership and any possible conflict of interests must be mentioned in the publication. The research reports that do not adhere to the principles described in this Declaration must not be accepted for publication.

(2) Both authors and editors have ethical obligations. To publish the results of his research, the researcher is obliged to maintain the accuracy of dates and results. Results must be published whether negative or positive or alternatively must be available to the public. In the publication it is necessary to cite the sources of finance, institutional affiliations and any possible conflict of interest. Reports of research that do not conform to the principles described in this Declaration should not be accepted for publication.

(3) Both authors and publishers have ethical obligations. Publication must safeguard accuracy of research data and results. Both positive and negative results must be published or otherwise publicly accessible. Financial sources, institutional affiliations and any other possible conflict of interests must be included in the publication. Any research report that does not adhere to the principles described in this Declaration must not be accepted for publication.

27.1S The singular form of researcher is retained in 2 of the back-translations; the 3rd eliminates the issue altogether by simply stating 'publication must safeguard accuracy of...'. The meaning of the two is the same and this is a stylistic difference only. However, it is an unnecessary difference and with a minor change there could be closer harmony between the two versions.

27.2S One back translation translates in error 'dates and results'; the other two preserve 'data and accuracy'. The reason for adding data is puzzling. Accurate results would be impossible without accurate data so safeguarding the accuracy results covers both. We suggest that the words 'datos y' are an unnecessary change in the Spanish version.

27.3S 'Se debe citar' is variously translated as 'must be mentioned', 'it is necessary to cite', and 'must be included'. The range is so broad it probably defeats any argument that 'should be declared' and 'se debe citar' are really different in any significant way from one another.

Additional Principles for Medical Research Combined with Medical Care

Paragraph 28

English version (2000): The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

1996 version: II.6 The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

French version (2000): Le médecin ne peut mener une recherche médicale au cours d'un traitement que dans la mesure où cette recherche est justifiée par un possible intérêt diagnostique, thérapeutique ou de prévention. Quand la recherche est associée à soins médicaux, les patients se prêtant à la recherche doivent bénéficier de règles supplémentaires de protection.

1996 version : II.6 Le médecin ne peut associer la recherch biomédicale à des soins médicaux en vue de l'acquisition de connaissances médicale nouvelles que dans la mesure où cette recherche est justifiée par une utilité diagnostique ou thérapeutique potentielle pour le patient.

28.1F 'Medical care' in the English occurs as 'au cours d'un traitement' ('in the course of treatment') in the French version. 'Care' would seem to encompass a much broader, more holistic notion than 'treatment'. The word 'soins' would be available in French to encompass the broader notion and in fact is used in the 2nd sentence.

28.2F The word order 'prophylactic, diagnostic or therapeutic' in English becomes 'diagnostique, thérapeutique ou de prévention' in French. Given that there is a natural logic to the progression in the English order, it is perplexing as to why the order is different in the French version.

Back translations:

(1) The physician can lead medical research during a treatment only insofar as this research is justified by a possible diagnostic, therapeutic or preventive interest. When research is connected to medical treatment, the patients lending themselves to this research must benefit from extra protective rules.

(2) The doctor can carry out a medical research during a treatment only if this research is justified by a possible diagnostic, therapeutic or preventive interest. When research is associated with medical care, the patient who participates in the research must benefit from the complementary protection rules.

(3) The physician cannot carry out medical research while a subject in medical care unless the research is justified by a possible diagnostic, therapeutic or preventative interest. When research is associated with medical care, the patient having lent himself to research must benefit from the additional protection standards.

28.1F In two of the back-translations the word 'treatment' is used while the 3rd reverts to 'care'. This may be considered to show that there is considerable semantic overlap and that the use of a different word in the 1st sentence ('traitement') from that used in the 2nd ('soins') is a literary stylist choice to avoid repetition.

28.2F The difference in word order is preserved in all 3 translations. While it could be considered a minor anomaly, it is completely unnecessary and the logical progression of prevention first, then diagnosis, then treatment is disrupted.

Spanish version (2000): 28. El médico puede combinar la investigación médica con la atención médica, sólo en la medida en que tal investigación acredite un justificado valor potencial preventivo, diagnóstico o terapéutico. Cuando la investigación médica se combina con la atención médica, las normas adicionales se aplican para proteger a los pacientes que participan en la investigación.

1996 version: II.6 El medico puede combiner investigación médica con cuidados profesionales, siendo el objetivo la adquisición de nuevos conocimientos médicos, en el contexto de que la investigación médica está justificada por el potencial valor diagnóstico o terapéutico para el paciente.

No particular differences between the English and Spanish versions were found on initial analysis.

Back translations :

(1) Doctors can combined medical research with medical care, only as long as such research proves to have a justified preventive, diagnostic and therapeutic value. When medical research is combined with medical care, additional norms apply to safeguard the patients participating in the research.

(2) The doctor can combine medical research with medical attention, only to the extent that such research gives credit to a justified potential preventive, diagnostic or therapeutic value. When medical research is combined with medical attention, additional standards apply to protect patients who participate in research.

(3) Doctors can combine medical research and practice only if it is proven that the investigation will have a potential justifiable preventive, diagnostic or therapeutic value. When both medical research and practice are combined the additional rules will apply to protect patients that participate in the research.

No particular differences arise from analysis of the back translations of the Spanish version.

Paragraph 29

English version (2000): The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

1996 version: II.2 The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
II.3 In any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

French version (2000): Les avantages, les risques, les contraintes et l'efficacité d'une nouvelle méthode doivent être évalués par comparaison avec les meilleures méthodes diagnostiques, thérapeutiques ou de prévention en usage. Cela n'exclut ni le recours au placebo ni l'absence d'intervention dans les études pour lesquelles il n'existe pas de méthode diagnostique, thérapeutique ou de prévention éprouvée.

1996 version : II.2 Le médecin devra peser les avantages, les risques et les inconvénients potentiels d'une nouvelle méthode par rapport aux meilleures méthodes diagnostiques ou thérapeutiques en usage.
II.3 Lors d'un examen clinique – avec ou sans groupe témoin – le malade devra bénéficier des meilleurs moyens diagnostiques et thérapeutiques disponsibles. Cela n'exclut pas l'utilisation du placebo pour les examens pour lesquels il n'existe pas de méthode thérapeutique ou diagnostique prouvée.

29.1F Whereas the English requires comparison of new methods against the 'best current' methods, the French version states that the new methods must be compared against the best methods 'en usage' (lit. 'in use'). The English version is subject to a variety of interpretations – does it mean best method in existence globally or does it mean the best method currently available to those involved in the research? By saying 'en usage', it is arguable that there is a tendency to favour the latter meaning. Normally, in English anyway, if we talk of the best method 'in use', we would have to add the adverb 'anywhere' to give the connotation of a global meaning. It is not impossible that 'in use' would implicitly mean 'in use anywhere' but that would be less usual. However, the phrase 'best current' is not as clear. "Current" has a time element to it and therefore could be construed to be either to be best 'current' at this time but without any specification of place, i.e. what is now the best anywhere in the world. It is possible to interpret the phrase as being the best that the participants are currently using but this requires the same subtle addition of meaning involved in interpretating 'in use' as meaning 'in use anywhere'.

29.2F The French version literally translated says 'The benefits, risks, burdens and effectiveness of a new method should be tested by comparison with the best…' whereas the English structures the sentence differently by requiring that 'the benefits etc. be tested against those of…'. 'Those' functions as a demonstrative pronoun for 'the benefits, risks, burdens and effectiveness of the best current…' in the English version and this long phrase becomes the object of the sentence. The French version does not have a direct object. It merely states 'The benefits etc. should be tested …' and then adds an explanatory clause 'by comparison with…' The meaning of the two versions is, however, not altered by the change in sentence structure. It does however constitute an unnecessary difference between them.

29.3F As in Paragraph 28, the word order in English 'prophylactic, diagnostic and therapeutic' is changed in French to 'diagnostic, therapeutic and prophylactic'.

Back translations:

(1) The advantages, the risks, the constraints and the effectiveness of a new method must be assessed by comparison with the best diagnostic, therapeutic and preventive methods in use. This does not exclude either resorting to placebo or the absence or intervention in the studies for which no well-tried diagnostic, therapeutic or preventive method exists.

(2) Advantages, risks, constraints and efficiency of a new method must be evaluated by comparison with the best diagnostic, therapeutic or preventive methods in use. This does not exclude resorting to placebo, nor the absence of intervention in studies for which no proven diagnostic, therapeutic or preventive method exists.

(3) The benefits, risks, constraints and effectiveness of a new method must be tested by comparison with the best diagnostic, therapeutic and preventative methods being used. This does not exclude the use of placebo or the intervention in studies for which there are no diagnostic, therapeutic and preventative methods being used.

29.1F The back-translations all retain the terms 'in use' ('being used' in one case). The issue of the standard of comparator arm (where placebo is not used) has been a major issue of debate. Which version is preferable depends on the outcome of that debate. The purpose of this study is simply to illustrate how the different language versions differ and, where possible, indicate how they could be brought closer together where they do differ. In this situation the difference serves to illustrate a major point of debate over the ethical standards of research which the Declaration of Helsinki seeks to address.

29.2F The 3 back-translations all retain the difference in sentence structure. This does not affect the meaning. However the two versions could be more exact translations of one another if the French were changed to 'Les avantages, les risques, les contraintes et l'efficacité d'une nouvelle méthode doivent être évalués par comparaison avec ceux des meilleures méthodes diagnostiques, thérapeutiques ou de prévention actuelles' or if the English were changed to 'The benefits, risks, burdens and effectiveness of a new method must be tested by comparison with the best diagnostic, therapeutic and preventive methods in use'. (This of course also assumes the resolution of the choices offered by 29.1F in favour of the other language's version).

29.3F The change in word order is maintained in the back translations and for the reasons outlined in 28.2F, the English word order is preferred.

Spanish version (2000): 29. Los posibles beneficios, riesgos, costos y eficacia de todo procedimiento nuevo deben ser evaluados mediante su comparación con los mejores métodos preventivos, diagnósticos y terapéuticos existentes. Ello no excluye que pueda usarse un placebo, o ningún tratamiento, en estudios para los que no hay procedimientos preventivos, diagnósticos o terapéuticos probados.

1996 version: II.2 Los beneficios potenciales, los riesgos y la incomodidad de un método nuevo deberían ser comparados contra las ventajas de los mejores métodos corrientes de diagnóstico y tratamiento.
II.3 Cada paciente, incluidos los del grupo control si existiera, en cualquier estudio clínico, deberían tener asegurados los mejores métodos diagnósticos y terapéuticos probados. Esto no excluye el uso de placebo inerte en estudios donde no existe un diagnóstico comprobado o un método terapéutico.

29.1S In the Spanish, the standard of comparator arm is defined as the 'mejores ... existantes' (lit. 'best ... existing'). This version would seem to settle the debate we refer to in 29.1F in the opposite direction. The Spanish wording would tend to lead the reader to consider the standard of comparison needed to be the 'best one in existence'. Some may argue that implicit in the Spanish version is 'best existing in context' but that requires a fair degree of assumption. The more natural reading would interpret this as the best in existence.

Back translations:

(1) The possible benefits, risks, costs and efficacy of every new procedure must be assessed through comparison with the best current preventive, diagnostic and therapeutic methods.

(2) The possible benefits, risks, costs and effectiveness of all new procedures must be evaluated by means of comparison with the best existing preventative, diagnostic or therapeutic methods. This does not exclude the use of a placebo, or no treatment, in studies for those where there are no preventative, diagnostic or therapeutic procedures.

(3) Any possible benefits, risks, burdens and effectiveness of any new procedure must be compared with the best existing preventive, diagnostic and therapeutic methods. This does not exclude use of placebos or no treatment at all in studies where there are no preventive, diagnostic or therapeutic procedures proved.

29.1S Although one back translation has converted the Spanish phrase into 'best current' (i.e. same as the English) the other two retain 'best existing'. This suggests some degree of semantic overlap but there is still the stronger suggestion in the Spanish version that the comparator arm is the best in existence. The versions are not

as exact a translation as they could be and the issue of which version should change again depends on the resolution of the actual ethical debate.

It is also noted here that the Spanish version has introduced the adjective 'possible' before the 'risks, burdens etc.'. This would seem to be redundant as the very context of a research setting means that it is 'possibilities' (rather than certainties) which are being explored.

A comparison of the three language versions of the note of clarification to Paragraph 29 is included after the discussion of Paragraph 32.

Paragraph 30

English version (2000): At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

1996 version: No equivalent.

French version (2000): Tous les patients ayant participé à une étude doivent être assurés de bénéficier à son terme des moyens diagnostiques, thérapeutiques et de prévention dont l'étude aura montré la supériorité.

1996 version: No equivalent.

30.1F The English version calls for patients to be 'assured of access' whereas the French requires that patients be 'assured of benefit'. This seems to be beyond what any ethical code can require. It is only the potential benefit (through assurance of access) that can be required.

30.2F Whereas the English version speaks of the 'best proven' method, the French refers to the method 'which the study shows to be superior'. This difference is essentially stylistic although it could be argued that 'les plus éprouvées' would bring the French closer to the English or to use 'access to the ... methods which the study shows to be superior' would bring the English closer to the French.

30.3F The difference in word order between prophylactic, diagnostic and therapeutic already identified in Paragraphs 28 and 29 occurs here as well.

Back translations:

(1) All the patients who have participated in a study must be assured that, once the study is completed, they will benefit from the diagnostic,

therapeutic and preventive means whose superiority will have been shown in the study.

(2) Every patient who has participated in a study must be assured to benefit, when it is completed, from the diagnostic, therapeutic and preventive means of which the study will have shown the superiority.

(3) All patients having participated in a medical study must be assured that they will benefit from the best diagnostic, therapeutic and preventative methods.

30.1F The assurance of 'benefit' remains in all 3 back translations. This seems to be something beyond anyone's ability to assure and is therefore an inappropriate requirement. The notion of 'access to benefit' is preferable.

30.2F Two of the back-translations preserve the sense of 'show to be superior' whereas one simply renders the French version as 'best' method.

30.3F See above for comments regarding word order.

Spanish version (2000): 30. Al final de la investigación, todos los pacientes que participan en el estudio deben tener la certeza de que contarán con los mejores métodos preventivos, diagnósticos y terapéuticos probados y existentes, identificados por el estudio.

1996 version: No equivalent.

30.1S The Spanish version, 'deben tener la certeza de que contarán con los mejores métodos' requires that patients 'should have certainty that they can count on the best methods...' whereas the English version states 'should be assured of access to the best methods...'

Back translations:

(1) At the end of the research, all patients participating in the study must be assured that they will have the best tested preventive, diagnostic and therapeutic existing methods, identified by the study.

(2) At the end of the research, all the patients who participate in the study must have the certainty that they will count on the best tested and existing preventative, diagnostic or therapeutic methods, identified through the study.

(3) At the end of the research all patients must be certain that they will have the best proven and existing preventive, diagnostic and therapeutic methods identified from the research.

30.1S There is an interesting variety of back translations; two refer to the notion of 'certainty' and one uses 'assured'. This suggests that there is a great deal of semantic overlap between the two. However, the literal notion of 'having the certainty to count on the best methods' is less clear than 'assured of access to'. Does it mean having the certainty to count on receiving them (which is more akin to the English version) or certainty to count on benefiting from them. This latter is similar to the French version which gives rise to the concerns mentioned above.

The reference to the notion of the 'best method... existing' is also retained in the back translation. This was not identified as a difference on initial analysis.

Paragraph 31

English version (2000): The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

1996 version: II.4 The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

French version (2000): Le médecin doit donner au patient une information complète sur les aspects des soins qui sont liés à des dispositions particulières du protocole de recherche. Le refus d'un patient de participer à une étude ne devra en aucun cas porter atteinte aux relations que le médecin entretient avec ce patient.

1996 version: II.4 Le refus du patient de participer à une étude ne devra en aucun cas porter atteinte aux relations existant entre le médecin et ce patient.

31.1F The French version requires that patients be informed which aspects of their care relate to the 'protocole de recherche' (research protocol) whereas the English simply state 'which aspects of the care are related to the research'.

Back translations:

(1) The physician must give the patient thorough information on the aspects of the care linked to particular provision in the research protocol. The refusal of a patient to take part in a study must not, in any case, undermine the relations that the physician keeps with this patient.

(2) The doctor must give the patient complete information on aspects of medical care which are linked to particular aspects of the research protocol. The refusal of the patient to participate to a study should in no way damage the relationship between him and the doctor.

(3) The physician must provide the patient with complete information on the aspects of the care which is linked to particular dispositions of the research protocol. The refusal of a patient to participate in a study must not in any case interfere with the existing relationship between the physician and the patient.

31.1F The addition of 'protocol' in French is maintained in all back-translations. It seems an unnecessary addition and, although the meaning is unchanged, one or other of the versions could fairly easily be brought closer to one another.

Spanish version (2000): 31. El médico debe informar cabalmente al paciente los aspectos de la atención que tienen relación con la investigación. La negativa del paciente a participar en una investigación nunca debe perturbar la relación médico-paciente.

1996 version: II.4 La negative del paciente a participar en el studio no debe interferer nunca en la relación con su médico.

No particular differences between the English and Spanish versions of Paragraph 31 were identified on initial analysis. Given that the Spanish and English versions do not mention 'protocol', perhaps a change in the French to '

Back translations:

(1) The doctor must fully inform the patient about the aspects of care related to the research. The refusal of the patient to participate in a research study must never disrupt the doctor-patient relationship.

(2) The doctor must inform the patient precisely of the aspects of the treatment that relate to the research. The refusal of the patient to participate in research must never disrupt the doctor-patient relationship.

(3) Doctors must inform the patient about anything in their medical attention which relates to research. If any patient denies his/her consent to participate in the research, the relationship between doctor and patient must stay the same.

The back translations do not identify any particular differences not detected on the initial analysis.

Paragraph 32

English version (2000) : . In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

1996 version: II.1 In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, re-establishing health or alleviating suffering.

French version (2000): Lorsqu'au cours d'un traitement, les méthodes établies de prévention, de diagnostic ou de thérapeutique s'avèrent inexistantes ou insuffisamment efficaces, le médecin, avec le consentement éclairé du patient, doit pouvoir recourir à des méthodes non éprouvées ou nouvelles s'il juge que celles-ci offrent un espoir de sauver la vie, de rétablir la santé ou de soulager les souffrances du malade. Ces mesures doivent, dans toute la mesure du possible, faire l'objet d'une recherche destinée à évaluer leur sécurité et leur efficacité. Toute nouvelle information sera consignée et, le cas échéant, publiée. Les autres recommandations appropriées énoncées dans la présente déclaration s'appliquent.

1996 version : II.1 Lors du traitement d'un malade, le médecin doit être libre de recourir à une nouvelle méthode diagnostique ou thérapeutique, s'il juge que celle-ci offre un espoir de sauver la vie, rétablir la santé ou soulager les souffrances du malade.

32.1F In English the 2nd sentence begins 'where possible, these measures should be made the object of research' which contrasts slightly with the French version 'Ces measures doivent, dans toute la mesure du possible, faire l'object d'une recherche' (lit. 'these measures should, as far as possible, be made the object of research'. Does 'where possible' have any different meaning to 'as far as possible'? Perhaps there could be a slight difference in meaning, but even if not, this still represents an unnecessary difference. The English version could easily be changed to the sentence mentioned above.

32.2F The English version, in respect of making such actions the subject of research specifies 'where appropriate' whereas the French uses 'le cas échéant' (lit. 'if necessary'). This seems a totally different notion from the English 'where appropriate' in that the English version seems to suggest publication unless there is some reason it is inappropriate (i.e., a sense that encourages publication) whereas the French seems to discourage publication suggesting that it only occur 'if necessary'.

Back translations:

(1) When, during a treatment, the established preventive, diagnostic or therapeutic methods prove to be non-existent or insufficiently effective, the physician must, with the enlightened consent of the patient, be able to resort to non-tried or new methods if he/she considers that these present hope to save the patient's life, restore him/her to health or relieve his/her sufferings. These measures must, as far as possible, be the object of a research intended to assess their safety and their effectiveness. Any new information will be recorded, and if need be, published. The other appropriate recommendations stated in the present declaration apply.

(2) When during treatment the established, preventive, diagnostic or therapeutic methods appear to be non-existing or not sufficiently efficient, the doctor, with the enlightened consent of the patient, has to be able to resort to non-proven or new methods if he judges that these will give some hope to save the life, restore the health or relieve the sufferings of the patient. These measures must, as far as possible, be the object of a research aimed at evaluating their safety and efficiency. Any new information will be recorded and, if need be, published. The other appropriate recommendations detailed in this declaration are applicable.

(3) When during the treatment of a patient, the established preventative, diagnostic or therapeutic methods show themselves to be inexistent or insufficiently effective, the physician, with the clear consent of the patient, must be able to use new or unproven methods if the physician feels that these other methods might lead to saving the patient's life, re-establish health or reduce the suffering of the patient. These measures must, whenever possible, be made the object of research designed to evaluate their security and their efficiency. All new information must be recorded and where appropriate, published. Other appropriate recommendations stated in the present declaration are applicable.

32.1F The back translations preserve the difference. 'As far as possible' (or 'whenever possible') has a different connotation to 'wherever possible'. It seems an unnecessary difference which could easily be corrected.

32.2F This difference is retained in the 2 of the back translations and one reverts to 'where appropriate'. It is a perplexing difference. What could 'if need be published' mean. Surely the issue is that such findings should be published unless it is inappropriate, i.e. the English version captures the ethical intention here. Our recommendation is that the French reflect the English with wording along the lines of 'Toute nouvelle information sera consignée et, où semble approprié, publiée'.

Note that here the French version follows the order of the English version with respect to prophylactic, diagnostic and therapeutic – it can be done!

Spanish version (2000): 32. Cuando en la atención de un enfermo los métodos preventivos, diagnósticos o terapéuticos probados han resultado ineficaces o no existen, el médico, con el consentimiento informado del paciente, puede permitirse usar procedimientos preventivos, diagnósticos y terapéuticos nuevos o no comprobados, si, a su juicio, ello da alguna esperanza de salvar la vida, restituir la salud o aliviar el sufrimiento. Siempre que sea posible, tales medidas deben ser investigadas a fin de evaluar su seguridad y eficacia. En todos los casos, esa información nueva debe ser registrada y, cuando sea oportuno, publicada. Se deben seguir todas las otras normas pertinentes de esta Declaración.

1996 version: II.1 El médico debe estar libre de utilizar una nueva medida diagnóstica o terapéutica en el tratamiento de una persona enferma si en su opinión la mima le ofrece esperanza de vida, restablecimiento de su salud o alivio en el sufrimiento.

32.1S The Spanish version uses 'puede permitirse usar' (lit. 'can allow him/herself to use') whereas the English version says 'must be free to use'.

32.2S Where the English uses 'where possible' to begin the 2nd sentence the Spanish version says 'siempre que sea posible' (lit. 'always when possible').

32.3S The English version reads 'these measures should be made the object of research, designed to evaluate their safety and efficacy' whereas the Spanish version states 'tales medidas deben ser investigadas a fin de evaluar su seguridad y eficacia' (lit. 'these measures should be investigated for evaluation of their safety and efficacy'.

Back translations:

(1) When the preventive, diagnostic or therapeutic tested methods prove to be inefficient or non-existent for care of the infirm, the doctor, with the patient's informed consent, can allow him/herself the use of preventive, diagnostic and therapeutic new or non-tested procedures, when to his/her mind, this gives hope of saving life, restoring health or alleviating

suffering. Where possible, such measures must be researched into in order to assess safety and efficiency. In all cases, that information must be registered, and where appropriate, published. All the appropriate norms in this Declaration must be followed.

(2) When in the treatment of an ill person the preventative, diagnostic or therapeutic methods tested have been ineffective or non-existent, the doctor, with the informed consent of the patient, may allow himself to use new or untested preventative, diagnostic or therapeutic procedures if, in his judgement, it offers some hope of saving life, restoring health or alleviating suffering. As far as possible, such measures should be investigated in order to evaluate their safety and effectiveness. In all cases, this new information must be registered and when opportune, published. All other relevant standards in this Declaration should be followed.

(3) Doctors, with the informed consent of the patient, can try new or unproven preventive, diagnostic and therapeutic procedures, if in the care of that patient all established preventive, diagnostic or therapeutic methods have been ineffective, or if such do not exist. Doctors can only try these if they think the new or unproven procedures may bring hope to preserve life, restore health or mitigate suffering. If possible these measures must be investigated to evaluate their safety and effectiveness. In all cases, that new information must be recorded and, if possible, must be published. All other standards in this Declaration should be followed.

32.1S The sense of 'can be free/can allow him/herself to use' is retained in the back translations and is different in meaning from 'must be free to use'. 'Deben que ser libres para usar' may be a closer translation. However, it may be a somewhat 'wooden' translation. Since both the English and French versions have the sense of 'must be free' however, some consideration should be given to bringing the Spanish version closer to them in meaning.

32.2S The back translations variously use 'where possible', 'as far as possible' and 'if possible'. It would appear that the Spanish version is not truly different from the English version in this case and no case can be made for change to one or the other.

32.3S The back translations do preserve the difference. Although there is not really a change in meaning between 'made the object of research' and 'investigate to evaluate' the two versions are not as exact as translation of one another as they could be. Since the French version more closely parallels the English version, we suggest that to harmonise the three the Spanish could read 'Donde sea posible tales medidas

deben ser usadas como objetivo para la investigacion a fin de evaluar su seguridad y eficacia'.

Note of Clarification on Paragraph 29 of the Declaration of Helsinki

English version (2000): The WMA is concerned that Paragraph 29 of the revised Declaration of Helsinki (October 2000) has led to diverse interpretations and possible confusion. It hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons it is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or

- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

1996 version: No equivalent

French version (2000): L'AMM réaffirme par la présente note que les essais avec témoins sous placebo ne doivent être utilisés qu'avec de grandes précautions et, d'une façon générale, lorsqu'il n'existe pas de traitement éprouvé. Toutefois, même s'il existe un traitement éprouvé, les essais avec témoins sous placebo peuvent être éthiquement acceptables dans les conditions suivantes :

- lorsque, pour des raisons méthologiques impérieuses et scientifiquement solides, il n'existe pas d'autres moyens qui permettent de déterminer l'efficacité ou l'innocuité d'une méthode prophylactique, diagnostique ou thérapeutique ;
- lorsqu'une méthode prophylactique, diagnostique ou thérapeutique est mise à l'essai pour une affection bénigne et que la participation à l'essai n'expose pas à des risques supplémentaires de dommages significatifs ou durables.

Toutes les dispositions énoncées dans la Déclaration d'Helsinki doivent être respectées, en particulier, la nécessité d'un examen éthique et scientifique approfondi.

1996 version: No equivalent

29ncF.1 The English version speaks of possible 'confusion' while the French version uses 'malentendu' (lit. 'misunderstanding').

29ncF.2 The English versions requires that 'extreme care' must be taken over use of placebo whereas the French version requires 'grande precautions' (lit. 'great precaution').

29ncF.3 The English version uses the phrase 'in the absence of existing proven therapy' as an adjective, whereas the French phrase is 'lorsqu'il n'existe pas de traitement éprouvé'.

29ncF.4 – difference no longer considered to exist.

29ncF.5 The English version, in the 2nd of the two clauses defining acceptable conditions for the use of placebo where proven therapy exists makes the requirements that there be no 'additional risk of serious or irreversible harm'. In the French version the requirement is 'des risques supplémentaires de dommages significatifs ou durables'. 'Durables' (lit. long-lasting) would seem to have a different meaning than irreversible. The adjective 'irréversible' is available in French or the English could be changed to 'long-lasting' depending on what the intent is. The Spanish version uses 'irreversible'. However, the ethical demand does need clarifying. If a harmful outcome of a study potentially lasted several years (but was eventually reversible) would that really be acceptable? Our suggestion is that the English and Spanish version should probably change to reflect the French.

29ncF.6 The French version re-iterates the necessity for 'd'un examen éthique et scientifique approfondi' (lit. 'in-depth ethical and scientific examination/review') whereas the English simply states 'appropriate ethical and scientific review. These are different in meaning and clarification of what is intended is required. If in all cases 'in-depth' review is 'appropriate' then the English version should be changed to match the French as this is a clearer statement of the requirement. It should be noted that the Spanish version also uses 'appropriate' (i.e. 'apropiada') so this would need to be changed as well if the French version were adopted.

Back translations:

(1) The World Medical Association has noted with concern that Paragraph 29 of the Helsinki Declaration (October 2000) is the object of various interpretations and possible misunderstandings. Besides, the Association reasserts that trials with the use of control subjects under placebo must only be used very carefully, and, generally, when there is no well-tried treatment. However, even if a well-tried treatment exists, the trials with

control subjects under placebo can be ethically acceptable in the following conditions:

- when, for pressing methodological and scientifically solid reasons, there are no other means able to determine the effectiveness or the harmlessness of a prophylactic, diagnostic or therapeutic method; or
- when a prophylactic, diagnostic or therapeutic method is put to the test for a mild ailment and that participation in the trial does not expose the subject to additional risks of significant or durable harm.

All the measures stated in the Declaration of Helsinki must be respected, particularly the need for a thorough ethical and scientific examination.

(2) The AMM remarks with preoccupation that the Paragraph 29 of the Helsinki Declaration (October 2000) is subjected to diverse interpretations and possible misunderstandings. The AMM furthermore reaffirms that trial with subjects on placebo must be used only with great precautions and, more generally, when no proven treatment exists. However, even if there is a proven treatment, trials with subjects on placebo may be ethically acceptable in the following conditions:

- When, for pressing and scientifically sound methodological reasons, there is no other way that allows to determine the efficiency or innocuousness of a prophylactic, diagnostic or therapeutic method, or
- When a prophylactic, diagnostic or therapeutic method is put on trial for a benign affection and the participation in the trial does not expose to extra risks of significant or lasting damage.

Every disposition detailed in the Helsinki Declaration must be respected, especially the necessity of a thorough ethical and scientific examination.

(3) The WMA reaffirms that Paragraph 29 of the Declaration of Helsinki (October 2000) is the object of various interpretations and possible misunderstandings. The WMA reaffirms that tests placebo witnesses must be used with great precaution and in a general way, when there is no tested treatment. Furthermore, even if a tested treatment exists, placebo witnessed testing can be ethically acceptable in the following conditions:

- when, for imperious and scientifically sound methodological reasons there exists no other means to allow to determine efficiency or the safety of diagnostic therapeutic and preventative methods; or
- when a diagnostic, therapeutic and preventative method is tested for a minor condition and participation in the testing does not expose the subject to other important risks.

> All the provisions stated in the Declaration of Helsinki must be adhered to, in particular, the need for ethical and scientific review.

29ncF.1 All back-translations retain 'misunderstandings'. While it is arguable that no confusion can ever exist without 'mis-understanding', there is a sense in English where misunderstandings don't refer to confusion so much as to conflict – e.g. two people had a 'misunderstanding'. Given the availability in French of the word 'confusion', this would not only be a closer translation but probably a more apt word for the situation. We suggest 'est l'objet d'interprétations diverses et peut preter à confusion' for the wording of this phrase.

29ncF.2 Two back translations retain 'great precaution' while one renders this passage as 'very carefully'. These seem sufficiently synonymous that greater harmonisation of the translations is not necessary.

29ncF.3 The back translations of this phrase are 'when there is no well-tried treatment', 'when no proven treatment exists', and 'when there is no tested treatment'. Although it could be argued that the phrase could be constructed such that the English and French were more exact copies of one another, these are synonymous with each other as they stand.

29ncF.4 No further comment on this.

29ncF.5 One back translation uses 'durable', one uses 'lasting' and the third paraphrases somewhat and says 'other important risks'. There is a clear difference in meaning between 'irreversible' and 'long-lasting'. We discuss above why the French version may be preferable from the standpoint of ethical intent and suggest the English be changed to 'serious or long-lasting harm'.

29ncF.6 Two back translations use the word 'thorough' to translate 'approfondi' while one leaves out any adjective. The notion of a thorough scientific and ethical review is probably always appropriate in a context of a plan to use placebo-controls where there is existing proven treatment. This we suggest, is the preferable version and 'appropriate' here is too vague and is probably redundant as who would ever suggest doing an 'inappropriate' review?

Spanish version (2000): Nota de Clarificación del Párrafo 29 de la Declaración de Helsinki La AMM reafirma que se debe tener muchísimo cuidado al utilizar ensayos con placebo y, en general, esta metodología sólo se debe emplear si no se cuenta con una terapia probada y existente. Sin embargo, los ensayos con placebo son aceptables éticamente en ciertos casos, incluso si se dispone de una terapia probada y si se cumplen las siguientes condiciones:

- Cuando por razones metodológicas, científicas y apremiantes, su uso es necesario para determinar la eficacia y la seguridad de un método preventivo, diagnóstico o terapéutico o;

- Cuando se prueba un método preventivo, diagnóstico o terapéutico para una enfermedad de menos importancia que no implique un riesgo adicional, efectos adversos graves o daño irreversible para los pacientes que reciben el placebo.

Se deben seguir todas las otras disposiciones de la Declaración de Helsinki, en especial la necesidad de una revisión científica y ética apropiada.

1996 version: No equivalent

29ncS.1 The English version refers to 'minor condition' whereas the Spanish uses the phrase 'enfermedad de menos importancia' (lit. 'illness of lesser importance'). However, there is no obvious Spanish equivalent which would be closer to 'minor condition' without circumlocution.

Back translations:

(1) The WMA reaffirms that extra care must apply when doing tests with a placebo and, in general, that methodology must solely be employed if a tested current therapy does not exist. However, tests with a placebo are ethically acceptable in certain cases, even if a tested therapy exists and when the following conditions are met:

- When for methodological, scientific and pressing reasons, its use is necessary to assess the efficiency and safety of a preventive, diagnostic or therapeutic method,
or,
- When a preventive, diagnostic, or therapeutic method is tested for a lesser disease not entailing an additional risk, serious adverse effects or irreversible damage to the patients receiving the placebo.

Every regulation of the Declaration of Helsinki must be followed, in particular, the need for a pertinent scientific and ethical revision.

(2) The WMA reaffirms that it is necessary to take great care when using trials with a placebo and, in general, this methodology should only be employed if an existing and tested therapy cannot be counted on. However, trials with a placebo are ethically acceptable in certain cases, including if a tested therapy is available and if the following conditions are met:

- When for methodological, scientific or urgent reasons, its use is necessary to determine the effectiveness and safety of a preventative, diagnostic or therapeutic method; or

- When a preventative, diagnostic or therapeutic method is tested for an illness of less importance that does not imply additional risk, serious adverse effects or irreversible harm to the patients that receive the placebo.

All the other provisions of the Declaration of Helsinki should be followed, especially the need for a scientific review and appropriate ethics.

(3) The WMA reaffirms that special care must be taken in research with placebo and in general this methodology can only be used if there is not a proven and existing therapy. However, even if there is a proven therapy, trials with placebo are ethically acceptable, if there are the following conditions:

- When for methodological, scientist and pressing reasons its use is necessary to determine the effectiveness and safety of a preventive, diagnostic or therapeutic method or
- When a preventive, diagnostic or therapeutic method is being proven for a less serious illness that does not imply any additional risks, adverse serious effects or any irreversible damage for patients who take the placebo.

All other regulations of the Declaration of Helsinki must be followed, especially the necessity of an appropriate scientific and ethical review.

29nc1.S The difference between 'minor condition' and 'illness of lesser disease' (to take one example) is generally maintained in the back translations. However, there does not seem to be any real shift in meaning and no obvious alternative to the Spanish version chosen. In general, it is probably best to leave the English as is rather than contemplate a change to 'lesser disease' or 'illness of lesser importance' because it would be a somewhat awkward construction in English.

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APPENDIX 7: FULL LIST OF INTERVIEW CODES

Full list of codes used in qualitative interviews:

IntroductoryRemarks
Paragraph29
Paragraph30
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Paragraph27
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Accessibility
Altruistic motives
Animal research
Anonymised research
Aspiration vs pragmatism
Authority of DoH
Belmont Report
Beneficence
Benefit to population
Boundaries of research
Children (research on)
Choice of end points
Chronic illness
Clinical judgment
Clinical trials
Compassionate use - access
Competing / conflicting interests
Confidentiality
Consent
Contextuality - local situation
Criticism of Declaration
Cultural issues
Declaration of Geneva
Deontology
Developed countries
Developing countries

Drafting of declaration
Effect size
Effectiveness
Efficacy
Efficiency
Environmental issues
Equipoise
Ethics committees
Ethics in comparison with law
European Clinical Trials Directive
Evidence-based medicine
Exegesis
Funding of research
Future of the DoH
Good Clinical Practice (GCP) Guidelines
Genetic research
Geographical considerations
Health service comments
Healthy volunteers research
Hippocratic Oath
Historical controls
Historical insights
Honesty of researchers
Human rights
International Committee on Harmonisation Guidelines
Identifiable information
Identifiable tissue
Identifiable vs anonymised tissue and data
Ignorance of Declaration
Individual vs science and society
Inducements
Information to subjects
Intellectual property protection
Interpretation
Justice
Legal issues
Length of Declaration
Marketing of pharmaceuticals
Monitoring of clinical trials
Named journals
Nazi Germany - medical experiments
Nocebo
Noninferiority vs superiority trials
Non-maleficence
Non-medical health research
Nuremberg Code
Ongoing access
Organisation – British Medical Association (BMA)
Organisation – Canadian Medical Association (CMA)
Organisation – CIOMS
Organisation – Council of Europe
Organisation - Department of Health (England)

Slippery slope arguments
Specific condition - Alzheimer's disease
Specific condition - angina
Specific condition - asthma
Specific condition - baldness
Specific condition - breast cancer
Specific condition - cancer – not otherwise specified
Specific condition – Creuzfeldt-Jakob Disease (CJD)
Specific condition – chronic myeloid leukaemia (CML)
Specific condition - cystic fibrosis
Specific condition - deafness
Specific condition - depression
Specific condition - diabetes
Specific condition - endometriosis
Specific condition - hay fever
Specific condition - heart failure
Specific condition – HIV/AIDS
Specific condition - Huntington's Disease
Specific condition – hypercholesterolaemia
Specific condition - hypertension
Specific condition - ichthyosis
Specific condition – left ventricular hypertrophy (LVH)
Specific condition - malaria
Specific condition - mesothelioma
Specific condition - multiple sclerosis (MS)
Specific condition – nasopharyngeal carcinoma
Specific condition - neural tube defects
Specific condition - obesity
Specific condition - osteoarthritis
Specific condition - ovarian cancer
Specific condition – chronic or acute pain control
Specific condition - peptic ulcer
Specific condition - rheumatoid arthritis
Specific condition - Severe Adult Respiratory Syndrome (SARS)
Specific condition - schizophrenia
Specific condition – Sudden Infant Death Syndrome (SIDS)
Specific condition - sleep disorders
Specific condition - stroke
Specific condition – tuberculosis (TB)
Specific research study
Standard of control arm
Systematic reviews
Translation (between languages)
Uncertainty of effectiveness of treatment
Useful quotations
Utilitarianism
Vaccine trials
Virtue ethics
Vulnerable groups in research

APPENDIX 8: SAMPLE INTERVIEW TRANSCRIPTS

The following three interview transcripts are presented as exemplars of interviews with one of each of the "Authors", "Medical Researchers" and "Expert Commentators". These are whole transcripts except where identifying information such as names, specific job titles and names of organisations have been removed.

These three interviews were chosen as part of the validation or triangulation process described in Chapter 6. As such they were chosen at random – and not chosen by me – avoiding the risk of a biased choice of exemplars. Serendipitously, the interviewees come from 3 different countries thus giving some breadth to the "geographical voice" represented in the transcripts.

A complete set of full transcripts will remain with the Departmental Secretary at the Clinical Pharmacology Unit, University of Edinburgh. Requests for further research using this data set can be made to the Head of the Clinical Pharmacology Unit (currently Professor David Webb: e-mail CPU@ed.ac.uk) and these will be considered in consultation with the author of this thesis.

INTERVIEW WITH AUTHOR NO. 7 (A7)

RC: Well there's so much that you I'm sure can contribute to this whole study of how the Declaration of Helsinki came to be in its present form. And as I mentioned I'll take you to a number of parts of the text. What I tend to ask when I'm interviewing people the two key words are your experience of the impact of the text not only on the conduct of research but on the debate around the ethics of research. And also given that it's only 3 years that it's been in place, your opinion regarding the likely future impact. But that's also got an added dimension in your situation because you have a background that many won't have because you were there as the text was put together so while I would value your views on those other things your experience and opinion if we can come back as well to your views on what was intended as the text took shape.

A7: Okay.

RC: So I'll leave it for general comments before I you to specific paragraphs.

A7: Okay. In fact let me take it in some time order. As I mentioned a moment ago, the World Medical Association is a representative organisation and therefore has a cycled membership, that is people serve for numbers of years and then cycle off and so anything that occurs in such a representative body represents not only the conversations that occurred proximate to any document but oftentimes conversations that occurred prior to and after. And to the degree that those conversations are not verbatim taped - and they rarely are - people's interpretations of what gets said prior to, during and afterwards. I had the tremendous honour of being on the World Medical Association for a number of years before the particular modifications of the Declaration came about. And I think, it's somewhat insightful to realise that there were specific issues that seemed to recur: placebos being one of them, as well as specific events such as pharmaceutical development in markedly underdeveloped countries, that raised concerns around the table. And the realisation over a number of years that in fact this historic and extraordinarily important document for setting out core values probably required a re-look. Not piecemeal which is what had been happening through specific conversations, but in fact, in totality. Now helping that along were some well-regarded and renowned ethicists - Bob Levine is one - who had both been personally, verbally... and in writing fairly critical of some of his perceptions of where Helsinki did and did not serve research well. What that said was that it wasn't simply 'the organisational leadership but it was the ethicists and the researchers who were saying "to some degree this no longer meets my all of my needs"'. So I think that... it was a

group of pieces and then a realisation as you combined those that it was the document itself that probably needed to be re-looked at. The World Medical Association then embarked on what at least for my tenure turned out to be one of the most problematic series of events that I saw them do. Because the Declaration of Helsinki is, frankly, a cornerstone and one of the best known pieces of work; in fact, one of the pieces of work that came from its very origins, the World Medical Association put together a workgroup composed not simply of World Medical members but... World Medical leaders I guess, but also ethicists from around the world. And went through tremendously dedicated and detailed evaluation of where the problems and the concerns were. What current practice, what the environment was. And a number of presentations to the Council which is the executive body of the World Medical Association...

RC: I was at the Council Meeting in Divonne last year to observe that.

A7: Okay so you've actually seen that process. And I think what became fairly clear was some conflicts. First of all, as with a lot of organisations, there were many people who had lots and lots of years of history and it would be [used example related to interviewee's own country's legal frameworks]. Okay, one of our key documents and suddenly I don't recognise it anymore... okay? Because of the fact that the re-write said there's not only some philosophic and some ethical issues to be raised, but frankly it's in an antiquated format and it's very organisation presents some problems. And so the first several presentations to the Council from workgroups literally would have transformed the Declaration into something not easily recognisable as our cornerstone document. And it became clear over actually more than a year that that was not acceptable. (6min36sec) And so the working party was dissolved and ...

RC: Not acceptable to the WMA or to a much broader...

A7: Frankly not acceptable to the WMA. They ... not the people sitting around that table ... but "they", their predecessors, had been the drafters. In many peoples' minds the Declaration of Helsinki is almost the same as the World Medical Association. And so to have your cornerstone document ... for all intents and purposes disappear was simply too big a step to take.

RC: Sorry I interrupted...

A7: No it's quite alright... fortunately I do all kinds of interviews (7min25sec) so you'll have difficulty dissuading me from where I was ... Anyway - that too is problematic of this. So the issue is on the table: were there changes, updates, or additions that needed in order to meet today's environment. And were there in fact some issues that needed a directional change. But frankly what was the acceptable protocol for today had changed. And so the next series of conversations were: can we make changes to the Declaration that address those areas of conflict, the updates and the potential modifications without destroying what's recognisable as the Declaration of Helsinki. And that was the stage at which a completely internal workgroup ... took on an attempt to do all of the rewrite. It was certainly not exclusively the realm of the workgroup. There were many presentations to broad conferences that included physicians, ethicists, others... there were many opportunities within the council to give progress reports and hammer and slice and cut an splice do all the things that one does in editing.

RC: And also the internet ... soliciting views...

A7: Correct put it on a web-site - and it actually went back to all those people who had served on any of those preceding workgroups and a much broader audience as well to say "here's your chance. Give us your insights" and again, not a one-time shot but it's a work in progress so please stay on-line and continue to give us feedback. And ... as one gets older one loses track of time, but that process actually I think took about 18 months. And ultimately brought it back, brought a final product back to the Council. Even then, my recollection is, that it was hotly debated and discussed. Obviously one of the good things about widespread dissemination is you know ahead of time where you are going to find the speed-bumps. (10min7sec) And every one of those issues was raised again as I recall at the last Council meeting. And some of them again in the final process - as the Council approves a document and it ultimately goes to the once annual congress which represents all of the organisations that are part of the World Medical Association. (10min27sec)

RC: Can you clarify something for me on the voting that happens at the Assembly? Just a question that I've had two different views on. One is that some countries have a large number of votes.
A7: Correct.
RC: Japan, and I think the U.S. have the most and then there's Germany and the U.K. and a few others but someone told me that for ethical issues, it's one country, one vote.
A7: No.
RC: That's not the case? And the other thing I've heard which I think is correct because it came from Delon Human is that a 75% majority is required to change an ethical document.
A7: I believe that is correct. And the number of votes, of course, relate to the number of members...
RC: Paid-up members...
A7: That are paid...
RC: Declared members.
A7: Declared members.
RC: But there's no difference in terms of the voting rules, apart from that 75 percent, between ethical issues and procedural issues.
A7: Correct. Other than the height of the barrier one must cross.
RC: I'm glad to have clarified that as there's some misperception out there...
A7: No... no. There are some things that I think probably don't advance the discussion and increase the opportunity for critics to say "see there's a problem". My recollection is that after the Council fairly vehemently voted down the last, and I said earlier a year but clearly these workgroups took longer than that, this may have been a 2 or 3 year process with much more presentations to the Council. When in Chile? Either Chile or Uruguay, the last workgroup presentation was made and the Council vehemently, overwhelmingly turned it down. I recall approaching Dr. Human and saying that the issue is too important to allow this last very ... frankly my vocabulary has disappeared - ... it was a very heated and somewhat angry interchange.
RC: The Council meeting?
A7: The Council meeting yeah which included some visitors making a presentation. And that's not the way you want to leave your cornerstone document. And the fact that that format was ... appeared to me to be... one of the single biggest stumbling blocks. And somehow whether we use block paragraphs or indentations to me isn't the issue here. I too have an acquired love for an interest in ethics and so it was clear to me that these issues were far too important to be simply allowed to be put on the back burner because we didn't like the presentation... the format in which it was presented. So I remember approaching Dr. Human and saying, "why don't you appoint a small group and make sure it's got some different perspectives on it". [An identifying sentence removed – does not alter meaning of paragraph]
RC: And then what happened in Edinburgh?
A7: At Edinburgh we, again, this 2 years was kind of brought together and the Council after some heated debate approved it, took it to the assembly and in the assembly there were 3 or 4 issues I recall being debated fairly vigorously but again a substantial vote for ... There was certainly even then, even in Edinburgh, both at the Council and at the Assembly were some strong voices in terms of opposition to some of the language that was coming forward. Those voices were vociferous enough that frankly ... none of them were voices I would have anticipated responding in a 'throw up your hands' that's usually a frustration/fatigue kind of vote, and we simply hadn't been carrying on all that long. But you know, who can climb into someone else's head and know why they cast a particular vote. I think there was also some magnificent rhetoric about the historic and ongoing importance of the Helsinki document, as has appeared frequently since - about the fact that global principles often are then tag-teamed, put side-by-side with, much more explicit detailed process if you will.
RC: So the CIOMS type of document or the ICH document?
A7: Exactly and both because of the history and where the WMA wanted to remain then it was important, once people had in fact decided "okay the document's going to go forward", it was

important that it not go forward in a terribly conflicted manner. So perhaps there was some magnificent rhetoric that somebody would say "okay if I can't win my issue then I'm not opposed enough to block the passage of this". But again you'd have to go back and talk to the 60 or 70 people who voted.
RC: And the note of clarification, the subsequent note, were you involved in the drafting of that?
A7: I was not. Edinburgh was actually my last meeting. I was aware it was coming. And I was not involved but I'd probably have voted against it (laughs).
RC: Does this clarify paragraph 29?
A7: Depends on who you ask. I think it changes the paragraph ... Now to the researchers who don't like the language of paragraph 29 (19min08sec) as it appears in the Declaration, do they think the quote "Clarification" unquote, expounds upon the words that are there, perhaps so. Because what it does is it pushes the door much wider open and that, of course, is what their entire argument is for. As one of the authors, and had I been at the table as that discussion carried on, what I would have argued is, in fact, that paragraph 29 leaves the door ajar and that the intent had been that the door had been ajar and not gaping open but... again, you know, the process has to be respected in that the intent is to represent a widespread series of environments, series of legislative needs, as well as cultural interpretations.
RC: Before we go into the specific paragraphs, there's one last question that I was thinking I might leave until the end but I'll ask you now. You talked about the Declaration as a cornerstone document. Some have now said it's influence is waning. I know Robert Temple at the latest assembly referred to the fact that it will probably be removed any reference to it will probably be removed from FDA rules and regulations others have seen the rise of the ICH document and the European Directive on Clinical Trials and that sort of thing and say that it's influence is waning. A view on that opinion?
A7: I think that probably in terms of setting again the ... I find myself motioning an "umbrella" but I think I actually mean a "foundation" for ethical principles - I don't think it in any fashion is waning. In fact its very importance in terms of driving policy, regulation, and even other guidances, like CIOMS, is demonstrated, I think, by the vehemence with which the discussions have continued. Again, I suspect some of us will seek out opportunities to argue that it should not disappear from references like FDA regulations. But the reality is that whether it appears in FDA regulation or not, the principles set forth I think continue to thread through regulations, guidances, and others. So no I don't think its...
RC: Do many [ethics committees in interviewee's country] still have some reference to the Declaration of Helsinki and that research should comply with the principles laid out?
A7: I know that some do and I honestly have not either done or seen research to quantitate that for you.
RC: Do you know about your local ethics committee?
A7: I was afraid that question was coming - I don't.
RC: Don't worry about it. Ours has actually declined to update it and still refers to the '96 version when they refer to the Declaration of Helsinki because they're nervous about
A7: The placebo?
RC: No I think paragraph 30
A7: Oh the follow-ups...
RC: They're also nervous about the fact that it's still in contention and may change so they're going to hold off.
A7: But again you see, I think that very comment suggests to me that it isn't waning so much as we're clearly in a period of transition that says "you know: did we miss the mark?" And you don't throw out the baby with the bathwater, you don't throw out the Declaration you continue to say, okay my perspective is - if 29 is too rigid for some, and the clarification is too flexible for others, is there someplace in between where we need to be? I don't think you throw out the Declaration, you simply realise in fact that you somehow find the appropriate moral, ethical guidance that also is liveable with the day-to-day functions.
RC: Acts as a mediating text?

A7: That's right.
RC: Okay paragraph 29? We did touch on that before and I've got the paragraph here, and its note of clarification and the previous version and a number of questions arise to me. One is that there's been a furore about the 2000 version and yet when you read the previous version, and even the versions before that when the placebo wasn't mentioned but there was "should be assured of the best available... the best proven": this one [1996 version] of course mentions placebo and says it should only be used where active treatment doesn't exist and then this one [2000] came along and then there was the furore that led to the clarification: why not after '96 or even earlier?
A7: I think because, in 1996, had you done a study and asked people to interpret what that means, there is enough grey that people who have raised the furore about 29, the 2000 version, can kind of wriggle through the cracks if you will. In fact, one of the arguments that has been raised recurrently through the last 3 years is that despite what the 1996 version said, placebo use has continued, the FDA continues to demand placebo studies and what happened in 2000 is the language was "cleaned up" – my term - so that in fact I believe there is still room for placebo studies. There's just a little less room for someone to self-interpret where one can use placebo studies. So if you believe you're committed to following the ethical precepts laid out by your profession, now you may find yourself with a conflict that you were able to talk yourself out of before and the clarification makes it a little tougher. I, like you, believe that 29, 2000, and that language in 1996 say the same thing: but, were I looking for an excuse to do placebo-controlled studies, I might like the previous somewhat less explicit language.
RC: When you drafted this did you have the kind of me-too, non-inferiority studies in your sights saying "those are the things we want to start to put restrictions on and we want things tested against controls".
A7: Actually no. Well that's not fair - yes we did talk about the me-too studies, not in terms of targeting them so much as saying the difficulties with what we do with me-too and non-invasive or non-... what's the clarification call them... (reads) where there's no additional risk of harm okay. So that ... antihistamine studies if you will, recognised and talked openly about the fact that that question was going to be raised. But what actually drove us was "where is medicine in the late 90s and what are the real issues facing us?" And what we recognised was that 29 doesn't, in any fashion, change what you do about a brand new technology or pharmaceutical. What it does address is the fact that today we are saying to physicians we need to use best practices evidence-based medicine and, by the way, the cost of intervention a, b and c are in fact a very important piece of the equation as you're sitting down with a given patient. It's true with the industrialised countries where you see Canada and Great Britain struggling with having enough money to pay for their systems (28min08sec). It's true in the United States, which is spending one and a half to two times what Canada and Great Britain spend per person or per percentage of GNP and yet still has 43 million uninsured people. So in 2008 we had some interesting conversations ... and that doesn't even touch upon the huge percentage of the world population that has access to only a fraction of what you and I would consider imperative medicine. So cost is important. And, where you choose to spend it. And what we came back to time and time and time again was... it's not helpful to the patient, or to the teacher, or to the practising physician to know that the newest blood pressure drug, antihistamine, diabetic intervention is better than a sugar pill. What I need to know, is from a risk issue, from an effectiveness issue, from an acceptability to my patient issue, how does it compare to what I'm using today? Interestingly, it brings us right back to where we were in 1996 which says you must give me a reason to use placebos. Now if you listen very carefully, read very carefully the arguments, the furore raised about 29, version 2000 they tend to come down to "do you realise how much more expensive those studies would be to do?" But no demand that we stack up two sets of dollar bills if you will, or pound notes, and say that the research will cost more but my goodness, the savings in therapeutics is going to be 20 times.
RC: The other argument I've heard there is that you also have to enrol a lot more patients and in theory with a new compound and not every risk is predictable, you are exposing a larger number of people to the unknowns of that new compound...
A7: And my response to that I guess would be... that whether you expose those people to the risks of the compound, and by the way, it doesn't matter if it's a new compound or an old compound,

the early portions of the study are to expose small numbers of people so that you identify the really dangerous risks. You need only look at the last decade of the FDA to know that in fact you don't find all of the risks, whether it's a placebo-controlled study, or an active-controlled study, until you begin to look it in tens of thousands of patients. So you might even argue, okay, that this concept of signing up more people in an active control study where there's going to be much closer supervision than what you get in my private practitioner's office, is a much safer way to evaluate this new drug than to simply test it, know how it performs against an inert compound and then hand it to every practitioner who has access to a prescription pad. It is more complex science. It is more complex metrics. Is it equally as good? Is it phenomenally better? Is it only marginally less good? And the statisticians, in fact, have made very good arguments that it is statistically and numerically and probably cost-wise, much more difficult to do the research. We as taxpayers, we as philanthropists, and those of us who buy pharmaceuticals and recognise that somewhere between 15 and 40 percent of what we spend goes into research and development should be asking ourselves whether we want the results of those studies to tell us whether we change to the new drug or stay on the old drug as opposed to "do you want a pink pill because it's brand new or do you want a purple pill that we've been using for 10 years?" And the answer is that as long as you continue to placebo-control rather than active-control drugs it will take us many many years of a totally different kind of research in order to get those answers. Because they simply won't be done. It's cheaper, it's faster, it's easier to do a placebo-controlled study and therefore get it out on the market and protect your patent on the way.

RC: Well let me push you a little more on this because I might as well set up the interlocutor sort of thing with some of the things that the pharmaceutical representatives have said...

A7: Okay...

RC: One of them is that it does oversimplify the question to say "we're just comparing you know head-to-head trials to say which one's more effective because you might have say a non-steroidal that causes a certain range of side effects, certain patients don't like, and if you get another one quickly on the market that has a different range of tolerability and it's shown to be non-inferior then it's there for those patients who get headaches with the other one or can't tolerate because of other side effects that they have". (33min26sec)

A7: I'm always a little careful when I am responding to question like this ... my last statistics courses was some time ago! But I believe non-inferiority are active-control studies right. So when you say if I can show that it has a different range of side effects than drug X and it's not inferior, you haven't shown me that it's not inferior you've simply shown me that it's more effective than an inert compound.

RC: Right. Well that's a very valuable response there in terms of the debate that's going on with these interviews that I've done. One of the other questions that often comes up is "okay, let's say we are doing active control trials, now what is this 'best current'?" What do you mean by standard comparator, that the actual control arm has to be the best current method.

A7: Well I think that is clearly one of the terms, "best current", that certainly leaves some room for interpretation. But I think the recognition is that medicine in 2000, health care in 2000, is changing at a rate of rapidity that no-one could have predicted in 1940. Heaven only knows the rapidity of change that you and I might experience before we close out our medical careers. So I think the best current is our best shot at saying "recognise that what the standard of care, what the best available evidence tells you is a changing target" and so ... let's take hypertension. I used the drug [name of older antihypertensive] for many years when I first came into practice. It now has maybe two indications. In fact, today's medical students wouldn't have any idea what I was talking about I suspect. But in 1980, it was one of the best current interventions. So what we're saying is "what is the standard?", "what is the evidence-base?" and I think there's some room for somebody being able to make an argument that this is the best there is.

RC: Now some have said that the difficulty that gives rise to is that if you go into the 3rd world, or even into, into a developed country but you're going into more rural areas, they don't have teaching hospitals there, that sort of thing, you're doing a study of what's best in that kind of setting say the 3rd world then if you're comparator arm is the best current, then it's not really answering the

question that... if you're wanting to say "does this cheaper alternative that this country could afford... if you have to compare it to the best current that's available anywhere, it's not really going to give the answer that that country needs because you actually know ahead of time it's not going to be as good as what's done at the Mayo Clinic.

A7: Certainly the goal of the World Medical Association, I think is to advance the quality and availability of health care worldwide. And so the ideal goal, as we're doing research, must be to answer what the best care ideally is. And in best, has to take into consideration side effects, availability, acceptability and cost as we talked about earlier. So there was in fact disagreement ... obviously within the Council and the Assembly and obviously continuing since. Does this prohibit doing research which says the best current, and I may be out of date on this, HIV treatment is triple drugs; that what that does is limit availability because such a huge proportion of people cannot afford that? So what in fact is the comparative by choosing either different combinations or cheaper combinations or fewer combinations. I personally believe that's a reasonable test to do because the reality is part of best is "we can afford it". The best treatment for degenerative joint disease may be a joint replacement. The reality is that you're simply not going to do bilateral joint replacements, hips and knees, for hundreds of thousands of people. So would we not want to do research on non-steroidals because we knew that we could surgically fix it that's foolishness of course. Actually I just read a lecture on cochlear implants which in this country [cost in country mentioned]. And we were talking about people who are either going deaf or as a result of illness or injuries suddenly become deaf and the miraculous use of this technology. But one of the students wisely said was "well what about the person who has presbycusis and is having difficulty functioning?" Suddenly there was this explosion of information about how you could use this for the elderly. And all I could look at in my head was "for goodness sakes – [cost] a pop and you're better to get two than one so we're actually talking [cost x 2] for a population, 85 percent of whom are going to develop the disease". I mean I would vote 'yes' any day if somebody said I've got something that I think will get you 90 percent of what a cochlear implant will do and we'll do it for [a fraction of the cost]. I'd do the research. So 'best' incorporates a lot. However, and I think this will come back again in one of the other paragraphs we're going to look at is it acceptable and I'm not sure this discussion belongs here but you can lift it is it acceptable to go someplace where there is zero available and therefore best is anything better than zero to do comparative research when the intent is to leave that site with zero and take that comparative research back to someplace where the comparator in fact would have been substantial. My answer to that is 'no'. Using some of the statisticians and researchers very arguments by the way and that is, I'm not sure that you can do the results of research done on a population with chronic nutritional problems, totally different environment, substantially different you know health culture and assume that you can translate that one-to-one to the general public. So, when I say go over to an undeveloped country and do AIDS research and tell me if intervention A which is not standard care in the [developed country] is better than zero, if your intent is to leave intervention A in the undeveloped country when you leave - sure. But if what you want to know is how much better or worse it is than standard intervention in the [developed country], then I think you ought to be testing it in the [developed country].

RC: Thank you. That actually will come up in another paragraph.

A7: I thought it might.

RC: Before we leave here and I'm aware of time and I don't want to ...

A7: We're okay ... you've come a long way.

RC: ... just also to get your comment on the contents on the note of clarification (41min40sec) ...

A7: In my opinion the note of clarification has gone so far as to substantially neuter the 2000 version of 29. I think always where there's compelling and scientifically sound methodological reasons, you simply have to be able to make the argument not to yourself but to peers and that would clearly be acceptable in my opinion in paragraph 29 as it currently exists. By putting it in as a clarification it invites one to seek methodological stumbling blocks in order to simply avoid the rigour of paragraph 29. Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition, there's probably no better laboratory than [a developed country] for evaluating the

economic impact of minor conditions. And so I would say again, it is not the severity of the condition that should dictate scientific rigour but it is the true breadth of what new and improved means and cost has to be a part of that. Neither my country nor any other one in the world can afford to advance without looking at the cost implications because we frankly endanger the advancement and the availability of the existing as well as the future health care for the entire world.
RC: Right...
A7: Now I ask whether you meant ... I think we addressed it to some degree, I ask whether there is not any additional ... oh that's for minor conditions, that's all.
RC: Someone has raised a problem ...
A7: With the 'or' instead of the 'and'?
RC: With the 'or' instead of the 'and' - yes.
A7: Well you know frankly they can make that easy - just take it out and don't put either one. Put the two exceptions to the rule and you can... I see them as two different things. One is I've got this sterling drug and I really want to do it but I'm not wanting to spend the money for the very large active control that would have to be done. Is that a methodological problem or is that simply a philosophic opposition to spending money on research? (44min27sec) I think I truly them as two different criteria and I think the 'or' for those who put it in makes it very clear you only have to meet one.
RC: That's the issue they raised. And many have pointed out, interestingly, that the 'or' would seem to suggest that you could have the second but not the first
A7: Right.
RC: But that would be wrong because that would say that it's not scientifically compelling and why would you do a placebo-controlled trial that's not scientifically compelling if it doesn't have a good scientific basis it's not ethical to do.
A7: Well because it's a minor condition I'm not putting anybody at risk.
RC: Yes, but some would say if it's bad science it's bad ethics.
A7: Well, no, it's good science, it's just that the methodology doesn't dictate it must be placebo-control and therefore because it's minor I should be allowed to do the cheap study because nobody is going to be hurt anyway. Nobody except the health-care delivery system and the economics of it.
RC: Okay I think we could move to paragraph 30 which is another... well it's still up for ... it's still under a workgroup's analysis.
A7: This one, of course, is new. It may have been distantly alluded to in some of the preceding but in fact as I recall this is a new issue put in this Declaration. And I think recognises in fact something that the entire industrialised world is aware in and that is it's a shrinking world. So what happens in [one country] impacts us 20 minutes later and not 6 years. And I think it begins to address that which I said a few minutes earlier. To the degree that anyone is going to be involved in a study and every study has some potential risks some of them minor, okay but I think we truly don't know how substantial those risks are often until much much later... So for example... I mean we've said for year "it's just an aspirin". Sure an aspirin which erodes your gastric lining. An aspirin which depletes your platelets... So every patient is going to take some risk and the whole Helsinki foundation is built on people who are going to be involved in studies are going to be protected and as you expose them to risk you do everything you can to address it. To be "assured of access to the best proven" meaning whatever you find at the end of a study and I think it just comes down to the ethics, the moral, not based on ... I'm not sure I can point to anything in medicine it's a humanity morality that says "you can't go out and take advantage of a population, thank them very much, and then go home and advance your own welfare as a result of it".
RC: And the argument that people come back with is: what if the population agrees with that. What if they say "yeah"?
A7: To me, I don't want to insult undeveloped countries, but the simplest analogy is I can get children to agree to a lot of things because they truly didn't get informed consent because they didn't have the capacity, the education or the linkages that would explain what all this poppycock I explained to them in my informed consent... so we do recognise in the informed consent section that

simply walking through the steps and saying the words and getting somebody to put their signature on the bottom of a piece of paper is not informed consent. So how do you explain to these people the concept of risk, the concept that we're going to gather information, we're going to invade their privacy, we're going to change their environment probably forever and by the way when we leave it's going to be with a thank you and a shake of your hand? I'm not sure that that is something you can actually get informed consent for.
RC: Okay.
A7: Maybe... maybe there's ... and maybe we need some research to answer that question.
RC: If they could... if and to your satisfaction or to the satisfaction... would that then be something that was... that took a different moral or... I mean if they weighed it up and they said "well it's not good that we won't have the antiretrovirals at the end but we'll have better trained nurses and doctors and we'll have had those 2 or 3 years of treatment" and they actually spell out all of the things that lead you to believe that this is a weighed-up decision.
A7: Well, let me think a few more minutes. .... Yes to the degree that the largest argument is that that population probably either hasn't been and maybe cannot give true informed consent, would probably be addressed by somebody being able to do the work that showed that in fact terribly arduous to get there but you could get informed consent. And I do believe firmly that although sometimes we make stupid decisions that's a bad word sometimes we make less than intelligent decisions that a free-thinking person who has the necessary information is allowed to make a decision different from what I think they should. So, yeah. Now there are some other issues I suppose.
RC: Well one of the ones that comes up is that some would say that's what an ethics committee is for - to adjudicate as to whether that informed consent is really possible in that situation? (50min41sec)
A7: I suppose my argument there would be that our ethics committees, to the degree which I meant a committee located over here, over here at the site from which the research is being coordinated – okay - is geared to answering questions about adequacy of the informed consent in a population they understand and they can say "yep this meets standard criteria because after all the people we interface with understand what this means". To the degree, and I know there has been discussion, I don't recall that any of it's in the document, about the need to have an ethics committee equivalent if you were, at the site at which the research is being done. I think my concerns there are not insurmountable but frankly more arduous than I would expect most places to go through. For example, you can't take a group who live in the urban environment with whatever the local equivalent of a college education is and allow them to give away the rights of a rural population. So somebody that performed the task of an ethics committee and truly did so from the perspective of the population and the culture, you might be able to address my concerns. But you still come down to whether there is a moral and for myself personally there is the question is whether I'm allowed to impose my morality on others whether there is a moral issue here of using a population and not recompensing either their risk or their investment.
RC: Now there's a few other issues that come up repeatedly when we talk about paragraph 30. And the first one I'll ask you is related to the degree of ongoing obligation and the others are related to practicalities about delivering this. And that is: does this mean for life? I mean surely you can't be saying you know whoever sponsored the study, whoever did the research now for life has to...
A7: ... and we had heated discussions about that, realising that depending on how you answered that you might shut down research frankly. No, probably something short of life. Something more than a week. So now we can narrow the distance. Again, I think what it comes down to is, if in fact, researchers, the research community begins to buy the necessity of valuing the population that becomes the study subjects, then in fact what's acceptable today maybe ... again like best practice... may become a moving target. You know an acceptable public education 150 years was you could do a little reading, you could cipher a few sums and you could sign your name. (53min49sec) Now we would frankly call that functionally illiterate today. And an acceptable public education in the [name of country & description of basic education] with a fairly substantial skill set. So is this a foot in the door, is it a start yes, probably. And what we define as ideal is probably far more than what would

functionally occur. But I think it is strong statement that says "Helsinki was intended to protect populations and not just populations of people who look and act like you do".
RC: Okay. Practical issues that have come up: and hypothetical situation where you have a drug - the old drug, drug A that's used for condition X. And you are the researcher that goes into this situation. There are two new candidate drugs for this condition and you are doing your trial and you find that drug B is the best of the three. You've done a 3-way comparison and drug B is the best. However, there were 4 or 5 other studies ongoing that have shown drug C to be the best elsewhere. Reading this literally it would seem to suggest that your patients are owed drug B even though there is knowledge out there that this one study may have been an outlier. And it didn't give the same results. I guess really I'm focusing it around the question that people often say "we don't usually accept the results of just one study and I'm putting it into a context of what happens then".
A7: Again, I think this comes down to the fact that very little of this research is done by intellectual midgets and so in fact it's of less ... answering for myself not the WMA - it is of less concern in that instance, that specific instance whether it's drug B or C or if you walked away from the 5 studies and said "frankly they look like they're pretty equivalent use drug A". Presuming there was a placebo-controlled study by the way and that A is better than nothing.
RC: Yes, we'll say that A is already 'best proven' according to the canons of evidence-based medicine.
A7: So I think you're right. I mean 'best proven' is rarely results of a single study. In fact it's one of my arguments with all this garbage that appears in the newspaper. Yes, today that's true, give me 6 months to do some research and I could probably change it 4 ways. But at the same time, best proven means at the conclusion of a scientific study, or studies, I think it means somebody able to justify why they chose drug A, B or C and make an argument of it. If overwhelmingly everybody says "that's just foolishness, that's not an argument". But I think in your case you could make a valid argument for either B or C. You could say B maybe there's differences between these populations and so at least until the next set of studies is done, B is best proven in this population. I think you could make an argument when we look at meta-analyses, that if you take the study population as a whole drug C. And the good news is you're valuing the risk and the investment of the study population. You're in fact defining the next several sets of studies that need to be done which is always the case in science. (57min29sec) We've almost never said 'well this is the be-all and end-all, we're finished forever'.
RC: Right, you've later in the document, or rather earlier told us we're not allowed to do that.
A7: So in this case it's not so much you choose B or C it's have you thought through the process of what 'best proven' is?
RC: I guess what people are objecting to is the phrase 'identified by the study'.
A7: But it doesn't say that. What it says is 'at the conclusion of the study, every patient entered into the study should be assured of access to the best proven' not the best proven at the conclusion of the study...
RC: No 'the best proven identified by the study'.
A7: It doesn't say that. Oh, it actually does doesn't it? I'm sorry. The phrase ... (reads). Um... good point. Yeah, using ... obviously using literal in that case and sounding like I don't know what I'm talking about you'd have to say in your example, drug B. Now, drug C hasn't been investigated in this population, is that right? No you did all three. So now you've in fact laid out the next study. Is there something different about this population?
RC: So do a B versus C or whatever.
A7: That's true. That's a good point.
RC: And people have made that that they feel that even... I mean it may be that they're trying to split hairs about the wording but also saying that these are... as I said I was moving from the moral into the practical issues that people have raised.
A7: Absolutely. That's a good practical issue. And I suppose I would say here and therefore demonstrate that no work in my opinion is ever finally finished at least until the author dies. It doesn't matter how many times somebody has read it. I mean I can have 6 people edit something and I will

pick up everything from a typo to a grammatical error. So - is that an error? I don't recall why we said by this study.
RC: I mean you could argue that that's the risk that these people took they took the risk with this drug. If somebody elsewhere finds that another drug is better then what we owe these people is what we found in this study.
A7: In fact, recall at the time we were doing the revision. We were in the midst of, or right on the tail end of, the discussions about taking the HIV studies into Africa. Looking at much-shortened perinatal dosages, single drugs versus no drugs, as opposed to the triple therapy that was accepted everywhere else. And so I do believe 'by this study' was intended to say, to the degree that you are going to take what is different than or, specifically less than, standard of care, and go test it in a new population and remember I said there are justifications for that in my opinion, because cost is a substantial, it should almost never be the driver but it still has to be part of the equation so if you went and did a single drug study, even though best proven on HIV is triple therapy, are you required to do triple therapy when you leave? No, I don't think so. I think what you've proven is that single therapy is better than whatever you tested it against.
RC: Right.
A7: And hence by this study we don't want to obligate you to... if you're saying that there's a population that has zero, and I can't afford current best proven, but in fact I'm not doing a study to advance my health care, I'm doing a study to say 'is this better than nothing?' then you've got to leave them with that which you've tested. Very inarticulately said but ...
RC: Last thing before we move on is that many have said 'hang on, this is not the point splitting hairs about this study, and what if it hasn't got its license yet and all that sort of thing that people say it's an aspirational statement. Its not meant to be read as legislation'.
A7: Thank you. You got it. I couldn't say it better myself. Ethical statements are almost... well almost always aspirational. They challenge all of us to reach for perfection. For a morality level that we probably all fall short of. So falling short of may not be the failure. Planning to fall short of... is not consistent with the standards set forth.
RC: There is a perception, and this is an interesting almost a transatlantic divide and that's why it's very interesting to hear you agree with the aspirational aspects of this is that there is a greater and I mean I haven't analysed all these yet...
A7: It will be fascinating. Well, I need to take a sabbatical and to do some research like you are because I find these questions fascinating! The obvious and the answer you get from a lot of people is to the extent we are a society focused on litigation, in fact when we set down something with the intent that it be aspirational it quickly becomes law and if you fall short of it you are subject to being sued. Oh I'm not running for office so let me just say how I feel. I frankly think that in allowing ourselves to act on that concern that what we do is substantially water down the route of professionalism. We say 'you know we best only write down those things we have a pretty high likelihood of achieving because we might get sued'. And the reality is, I believe, from hundreds of thousands of patient interactions in my own personal life that though our personal satisfaction with that which we do and aspire to do, and certain our patients' satisfaction by the role we play, would be enhanced by us saying 'we're human and we don't always get there, but we will never stop attempting to achieve...'
RC: And so you're articulating in many ways the way that ethics and the law sometimes diverge.
A7: Absolutely.
RC: Right.
A7: Absolutely, but I think in addition to that...
RC: Almost a separate thesis...
A7: And I'd love to come and study more ... in this country I believe we have moved away from professionalism not entirely but more than I'm comfortable with I believe we are rapidly becoming a profession of technicians. We take care of particular body parts. We have particular procedures that we do. We have done a very poor job for some time now in incorporating the fact that there's a human

body attached to these body parts. And you've got to communicate and you've got to understand there's a linkage and if you go tinkering with my heart, it has implications for my liver...
RC: And my emotions...
A7: Absolutely. And so I think part of it is, if you are a technician, you don't aspire to put the screw in the right place, you do it by George, we're not technicians and our patients are not automobiles. And so I think it's symptomatic frankly of serious problems.
RC: That is a much broader discussion which, I mean it would be very interesting if we have 5 minutes at the end to come back to.
A7: Yeah, wonderful.
RC: But let's look at paragraph 19 which occurs earlier in the document. It occurs in the basic principles applying to all medical research. These two, of course, are under the subsection of research and clinical care and this you've alluded to already so just looking for any further insight into the intent that was here and... (66min45sec)
A7: I think this is a much more overt...
RC: I better say it's paragraph 19...
A7: Paragraph 19 is a much more overt perhaps in several of the paragraphs as we begin to try to protect populations in addition to the individual subject, I think we begin to talk about again this globalisation. Most physicians, even I think most researchers, even if they are not physician-researchers, have grown up with the concept of not putting their subject at unacceptable risks. But this concept that peoples, populations in fact, are in some ways the research subject themselves, I think paragraph 19 begins to say. Again, you don't subject this population to risk if in fact your every intent is to only benefit population B.
RC: Some have said okay let's take that to its literal conclusion that means you could never do research on healthy volunteers, because your intent is not to benefit the population of healthy volunteers but people with the condition that the drug is being developed to treat.
A7: Well, unfortunately, our status today changes on a regular basis and today's healthy volunteer is tomorrow's recipient of health care.
RC: So the concept of population has that time...
A7: Absolutely... absolutely.
RC: Right, I guess that's what I was starting to explore is what you had in mind when you said population. Is it population of a country or is it a much more flexible concept than that.
A7: I think it is fairly flexible but I think the specific discussions had to do with the fact that again you don't subject people to risk from which there is never any intention they would benefit okay. But we all know, of course, that we must have healthy volunteers for some of our research otherwise we simply couldn't advance the healthcare process.
RC: Right some had raised that sufficiently that there was even talk of a note of clarification to say that...
A7: Oh heaven forbid. Again, if they wanted clarifications, maybe they need to go to some of the other documents and write regulations.
RC: Well that's... I guess in terms of paragraph 30, would you see there being room for notes of clarification to remove some of those obstacles that I've just referred to or is it better just to...
A7: To the degree that the language substantially, repeatedly in large groups, raises the concern, I think you must look at the language. To the degree that there are small, very outspoken groups who say "I read it different than you do", I would prefer not to see clarification because in fact if you get a thousand readers you can probably find a thousand nits to pick. But if in fact somehow the string of words you put together creates overwhelmingly, repeatedly, with lots of different readers the same issue, then you ... I don't like notes of clarification I frankly would say "so edit it. Take it back and fix it".
RC: Well, those are the 3 that have provoked most of the discussion and the rest I have chosen because they seem to me to be big changes. They haven't yet resulted in quite the same level of controversy and there may be others that you want to take me to at the end of the specific ones that I've mentioned.

A7: Okay.
RC: Paragraph 27 I think is... you know it's changed significantly. There's the added requirement to declare potential conflicts of interests. That occurs elsewhere, of course, to ethics committees and with patient consent. The real one that I'm focusing here is the "authors and publishers have ethical obligations ... that negative as well as positive results should be published or otherwise publicly available". Again...
A7: Of course we here all the time that there are far more negative studies than there are positive. As the sources of funding of research become more varied, there are potential conflicts with even whether you publish anything. And it's unfortunate but it's very clear both from example and from environment that there has been certainly measurable and my perception is... increasing pressures when funds related to the research ... generally pharmaceutical but there are probably other instances as well... fund the research to say "I'll fund your research. I want to see the results of your research but what you do with the results of that research, I get to second guess". So I think that... publicly-funded research I can't imagine anybody saying "you can't publish that". Now research that I fund out of public funds - other than the fact that you can't find anybody to publish... okay.
RC: And you've said here that publishers have ethical obligations and yet, as ethical guidelines for doctors, a publisher might say "I'm a journalist, you know, I'm not a doctor. You can't put ethical obligations on me, my ethical obligations are to sell more of this journal".
A7: Actually the reality is most of our medical journals have physicians as editors.
RC: Editors but not...
A7: Publishers... oh you're right.
RC: Some have actually said why didn't you put the word editors in there?
A7: I suppose we thought it was just kind of a continuum but I don't think we ever intended anybody to be left out on purpose. Again, I think this is an aspirational statement. I think this is intended to empower the person who wants to do the right thing. And to stop the person who's willing to blatantly do the wrong thing. But if in fact, I guess negative results that I think happen to be of interest, and I submit it to whatever the appropriate number of journals is and I cannot get it published, I mean I've done a reasonable job. Now these days by the way that's becoming less and less of an excuse because the reality is you can get things on the internet in a heartbeat. (73min04sec) You know that you couldn't get in the New England Journal, you couldn't get in JAMA but you can get the information it's out there. But the reality is, I think what it said was, let us give you some guidelines, and more importantly let us put a tool in your hand so when editors, publishers or others say to you... you can say "no no I can't go there".
RC: Now, paragraph 1: the opening statement you've obviously elevated to the initial, to be the first sentence in the document and I don't think many people are too worried about that. But then there's this sudden, overt recognition that medical research involving human subjects includes research on identifiable human material or identifiable data.
A7: As happens often, issues that are hot topics at the time probably end up putting language in. But hopefully in this case also are indicative not of a fad but rather how sophisticated medicine is becoming. We are no longer a society that only looks at whole organisms or even organ systems. But in fact our genetic data, our to some degree, some of the epidemiological identifiable public health data have some of the same implications; different kinds of risks but risk implications nonetheless. Interestingly enough, simultaneously with what we were doing with Helsinki were the discussions about Iceland that was actually doing some total population studies.
RC: But not only that they sold the database to a commercial enterprise.
A7: And so one of the hot questions periodically burbling up through the literature but right on the horizon at that time was "what do you mean by medical research?" And so this is one of the issues that obviously they couldn't have imagined in 1950 when the original was written, but is and probably will continue to be ... issues here were hot at the time as was the Iceland issue so I think that's all it is a recognition that medicine has changed.
RC: And many have said all it's saying it's just stating the obvious, what we knew along, that of course this constitutes medical research involves human subjects. There's three broad areas which get

further discussion. One is the criticism by some that you haven't gone far enough. Why did you not include anonymised research because if you insensitively use data about groups you can do damage in the same way that you could perhaps do damage to an individual if their data were disclosed. Was that discussed? Was there a specific reason why you…

A7: You. I think it was probably more a matter and remember the climate in which we undertook the re-write. And that was, we certainly don't want to lose our Declaration, nor do we want to lose our pre-eminence of it being the World Medical Association. (77min03sec) And then the old-timers, the traditionalists said "well it has to at least look like the Declaration". Right. So the question was not can we cover the depth and breadth of every issue that might arise for science but can we take the issues that were key in accord of the Declaration of Helsinki, do the necessary modernisation, address some of the really writhing new issues that weren't there before, and I think anonymous data again I'm aspirationalist … and recognise best policies are not so specific that if it wasn't included in there it wasn't intended. So I would say you could probably take some of the misuse of anonymous data and be able to say "you see, this is research, it does impact individuals and these were not willing participants. Subjects in fact were damaged".

RC: The other things that have been discussed include: well I think it was Povl Riis who was one of the drafters of the '75, writing in JAMA raised the issue that "this is great it should be in there but the problem is that it hasn't had the ripple effect that it needs to on the other clauses about consent and things like that because there are different issues that arise". You ask an individual for consent for every time you do a clinical trial. You know if you're going to do another one later you ask them again. But if you have a stored piece of tissue or you have stored data, it is possible to get prospective consent. Now and there are ethical issues that come out of that and the problem is they haven't really been tackled by the sections on consent. One person even went to the extent of saying we should put these issues into a separate document and have Declaration of Helsinki is about clinical trials and then have a separate one about…

A7: Well, in fact I think that's not a bad solution. And I think I would come back to what I said. This is broad brushstroke aspirational lines. Whether it's World Medical, CIOMS, or national legislation, there in fact are literally thousands of issues that this touches upon. And some of them deserve their own paper that says "touched upon here and here it is in some depth". Some of them deserve a more legislative perspective guidelines, regulations, this is how thou shalt do it. And in fact in this country we have privacy regulations. We have seen a tremendous negative impact because of this concept of "is it consent every time I use that stored blood or that stored data? Or do I have to go back and get 20,000 people and get…

RC: Some of whom have died.

A7: Absolutely. And so our tissue banks and others are really struggling with interpretation. I think what the intent is again as you've got to look at the difference between say, constitutional law - a few pages long - and the libraries full of minutiae that attempt to apply that to every possible situation. This is best analogy.

RC: No, that's good. And really why I'm asking is "as the people who are putting this together what was in your minds and as you hear some of the issues that people have raised to hear what your response is well this is what were thinking etc." So that's why I ask, not to pick holes…

A7: No, I understand. I understand.

RC: Well we've not too far to go in terms of the specific paragraphs I'm going to take you to. Another dramatic change you took this and it went from being only a guide to physicians all over the world and they're not relieved from regulations and laws in their own country to this is now something that no national, ethical, legal or regulatory requirement should be allowed to reduce protections in this document.

A7: What drove that? Well part of that may be some of my experience in ethics and the [name of organisation] is very powerful statement in its principles, in its guiding piece that says "you know where there is a conflict between law and ethics, one has an obligation to attempt to change the law". And perhaps it's also a recognition, or a demonstration of the maturation of the organisation. When originally written it was an infant organisation, the world was coming off of this unbelievable

revelation of the atrocities committed and statements I suspect were much softer. You know, what repercussions are there going to be? The reality is I think a recognition that we should in fact empower maybe obligate physicians, researchers okay to say it's not simply that you can, it's that we're setting a standard and it may be it's aspirational again it may be that the laws in your country aren't there but then you have some obligation to try to get them there. It may be that you undergo some employment issues and you fight over this with your editors or whatever but as we set this up as a standard you do have some obligation put some energy behind this.

RC: No that's... the other point that's come up, that many observers have said is that ... I mean where they really see this as targeted is countries where either there's very little framework or they are undergoing rapid change and the example that's often given is Eastern Europe after the collapse of the Soviet Union. (83min24sec)

A7: Sure.

RC: And when suddenly there was not much, they were rebuilding whole systems and that this gave doctors, if they were in that environment... was that what you had in mind?

A7: Well it was clearly part of it, okay. We had people - not at the Council as I recall - but certainly at some of our seminars and presentations that said "if it's in the Declaration I have an opportunity to go to my legislators and say 'here's the standard'". We also, I think, had examples of where laws have been changed as a result of what was in an ethical... in the Declaration in particular. We obviously had examples in Germany, the United States and other places where the Declaration was referred. Now one of the discussions in fact was, "now wait a minute the law was passed in 1990 so if the regulation says I have to abide by the Declaration of Helsinki is it 1990 or now?" Fascinating conversation and so I think it was all of those things that said you know doctors are leaders and the World Medical Association is an organisation of leaders and changing the impetus, changing the onus here has the potential of changing the level of protection worldwide.

RC: Well thank you. That's ... I mean ... clarified a number of those issues. Okay this one I find fascinating. You have completely added the 2nd sentence there "even the best proven prophylactic, diagnostic and therapeutic methods must continuously be challenged through research..."

A7: This actually arose following very interesting, articulate discussions in the Council about the fact that the language especially paragraph 29 the language throughout the Declaration would potentially put a quietus on the ...

RC: What was that word you used?

A7: Quietus. There you go.

RC: Quietus... Shakespearean word.

A7: Is it? ... on ongoing research. That once you had best proven you did nothing more. Well best proven is only good for the day that the study comes out and the document is published. The reality is that this is a moving target. And so lest anybody be concerned that once we had a study that said X is good we want to assure that in fact there is always a need, whether you are looking for cheaper, easier, better I mean we had very good antibiotics and one of the challenges during the '80s and '90s wasn't necessarily that you needed a drug that killed bacteria X. It was the fact that people wouldn't take something every 4 hours. In fact we would tolerate side effects, as long as we could only take one pill a day. Now can you tell me that the antibacterial is any better. Well, yeah if I take it. Okay, so I think this statement was clearly both to address those people who said "I mean you're just going to put a stop to research". Well don't be foolish, but in case you actually believe that let us tell you okay?

RC: I'm interested in how you chose those 4 criteria.

A7: Well again, the possibility could be for an extraordinary litany. But as you talk about evidence-based medicine. As you talk about best interventions. In fact as you go to the quality literature, these are the words that come through recurrently. Certainly effectivness. Efficiency which addresses cost, which addresses frequency of dosing. Accessibility I contend is probably going to move to the front of that list pretty soon. Because the issue is it's no good if you know how to do it and no-one can have it. And quality I think because again there's another string of metaphors that people would be able to say well "quality is... these kinds of things". So they're to some degree words

of their time; recognition of where we are in this particular decade or two of health care. But I think they also in a fairly efficient way incorporate a whole string of potential.
RC: Many have said "I'm missing safety" why isn't safety in there?
A7: Ah well I think that most would say that safety and quality are in many ways synonymous. You can't read quality literature without seeing safety ... even I, who... have a penchant for stretching for the sake of application, think that probably safety best fits under quality.
RC: Some have said that you could probably fit it into effectiveness because if it makes you sicker than it makes you well, then it's probably not effective.
A7: Maybe, maybe.
RC: Thalidomide was pretty effective as a treatment for morning sickness.
A7: Yes it was. Just at a little high a price. That's interesting I didn't know that.
RC: This is very nitpicky but I think it was quite an interesting one the word continuously said should really be continually because if you read that, neither you nor I should go to sleep tonight, we should be up all night thinking of ways we could improve...
A7: (laughs) I would have to go and get my dictionary and see the parsed definition. That's probably true.
RC: Again it's giving a chance to say "no but continuously to us meant..."
A7: Aspirational ... and the reality is when I'm sleeping you're working and when you're sleeping somebody in Japan is working.
RC: So this is the profession as a whole...
A7: Yes. You and I do not have to commit ourselves to non-stop.
RC: Okay that was the last of the specific paragraphs I'm going to take you to for comment at the moment. Now the new structure. You've already mentioned this earlier on this is just a chance to add anything that you'd like to add...
A7: Interestingly enough, this was probably as much as anything we did in some ways an overt compromise as I'm sure you heard yesterday or the day before from Bob Levine my goodness these were archaic and impossible separations. Separations that obviously made sense in a time, but I wasn't there to hear the conversations. And at the same time remember probably the single issue that caused the original workgroups to fail was the... "actually it doesn't look like the Declaration of Helsinki I can't find my favourite paragraph anymore". So, it had to look like the Declaration of Helsinki both if you glanced at a piece of (90min46sec) paper and in terms of its core content. But Bob Levine and others had a powerful argument that in fact you simply can't separate out these two issues not in anything resembling a clean fashion. But in our minds there were some nice global phrases. The beginning says Introduction. There were in fact some principles that applied just across the board to research and then there were some very special things that happen when you're doing research to someone who is simultaneously a patient and a subject of research. The nice thing was it's a very nice continuum. It's easy to walk through the process I think. It very nicely looked a lot like the old Declaration. And yet we hoped ... what it did was do away with this artificial separation. In fact, these principles apply to any research healthy volunteer, patient, we don't care. But when you're dealing with a sick person, everything from the informed consent to how much risk they should have to take or be willing to take if there's nothing else to offer them, may change. And so it had all sorts of both justifiable and maybe very superficial reasons.
RC: Well some have raised the issue, and I must raise it with you as one of the committee that organised this - they're concerned about the disappearance though of a section that looks after the interests of healthy volunteers because sometimes they are recruited differently, they're paid for their participation there are differences between ... that perhaps should have had some specific recognition. Was that considered?
A7: I think what was considered because the healthy volunteer issues are all within that category called basic principles is that there... certainly there are lots of issues, in fact to some degree it was healthy volunteers that perhaps led to ever having a Declaration of Helsinki because we probably didn't think of it as being a volunteer if you were sick and we didn't have anything else to offer you, why not?

RC: Yes.
A7: And so everything in section B, the Basic Principles, applies to healthy volunteer. Now again, if you go back to specific paragraphs, where periodically you're talking about risk ratios, risk management, there are probably higher risks with a healthy volunteer who's doing this for a few pence, or out of the goodness of their heart. You say "how much risk should you subject somebody to?" As opposed to, when you get down to somebody who says "I'm going to die anyway". And then, of course, someplace in between maybe you've got the family member with the inheritable disease who says "yeah, I'm maybe putting myself at risk but after all I've got children, grandchildren, nieces, nephews who are likely to face this". So the perception was in fact, I believe, I think we overtly had this conversation, that there are lots of things you must do for healthy volunteers but virtually nothing that you must do for healthy volunteers that you only do for healthy volunteers. But there is in fact a small group of things that you don't have to do with healthy volunteers but you must do if it's a patient.
RC: Well you can use placebo studies freely with a healthy volunteer as one example.
A7: More effectively.
RC: Two questions remain: one relating to the text and that really is to give you a chance to bring up any issues of changes ... there's a lot obviously I haven't referred to, just so that one day I can finish this project; but there may be things that you want to draw my attention to that you think I've left out that are very important. (94min53sec)
A7: Well interestingly enough some of the very issues that are raised in the Declaration perhaps need to be raised even as you are doing your research and the debate continues and that is, I think it's imperative that the perspective, the environment from which some of the arguments are raised needs to be put out there. If you have conflict of interest it's only fair. If, for example, you are a researcher and the vast majority of your research is funded by a pharmaceutical company, it might cause me to look at your remarks somewhat differently than if I think your research is all coming from an academic institution no strings attached. Even regulatory agencies, because of chronic underfunding or whatever, who approves new drug applications and both helps devise some of the things that are necessary in research before a new drug is looked at and judges the outcomes of that research; and regulatory funding is largely dependent upon the fees that are paid by the companies that are submitting the new drugs, okay. Is that a conflict of interest? Frankly I believe it is. Is it insurmountable? But I think it only fair that the people who are going to weigh in, whether it's with notes of clarification, or with modifications, or sticking to their guns with the current language, ought to be able to have a full range of information with which to make their decision. So that's one of my concerns. Another of my concerns... yes, of course, and as with most ethics we can set forth the expectation but all too often unless something goes awry, all too often we have to count upon your good graces because we can't please everybody. But in fact I think there are instances where some of the spokespeople are largely funded by pharmaceutical companies, and I am not... I think I have many friends among the pharmaceutical companies. (97min26sec) I support increased dollars for research and I think pharmaceutical companies have in fact contributed to some of the advancements, many of the advancements that have been made in health care delivery. But I am not foolish enough to believe that they are not highly motivated by an extraordinary bottom line. It's a cash business for them frankly. So when a researcher says to me, it's insurmountably expensive to do an active trial, what I want to know is insurmountable to whom. Insurmountable to the publicly-funded bodies? Insurmountable in that you don't want to stick around long enough to do the trial? Or is the holder of the licence, the potential patent, simply not willing to invest the dollars.
RC: Okay conflict of interest and...
A7: Again I think probably because we have such a wide population, one of my frustrations and maybe I am simply demonstrating my own naivete okay I think we have some researchers who are a little fast and loose with their statistical arguments about what can and cannot, what should and should not, what must and must not be done. And frankly are counting at least to some degree on the statistical naivete of many of their opposers to not be able to say "you're absolutely wrong about that particular issue". That's a little gamesmanship and maybe I'd play it if I had the tools to do it. I think

probably ... you have actually said most of the words that I would have said in general comments. I think ethics are almost always aspirational. I think those who attempt to set guidelines for a group are falling way short of where they should be if they ever set them as easily attainable. I think by nature they should in fact require a little stretch and a little reach; maybe a little discomfort now and then. And I think Helsinki is clearly aspirational. I think wherever possible we should try to be sure that it is not absolutely in opposition to the more regulatory detailed guidelines but where it is I think we then should have that very difficult discussion. What in fact is the right thing? What should be aspiring to even if we have to acknowledge it's going to take us some time to get there.
RC: The last question: and this is not directly related to the text at all. It really is to help me interpret the things that people have said on the tape and it's I mean I'm obviously interviewing people from a variety of countries, a variety of disciplines...
A7: Backgrounds yeah...
RC: Backgrounds. And it's really a moment's self-reflection.
A7: Okay.
RC: The question is: how is it that you have come to hold the views that you hold about these things and have expressed on the tape? (100min36sec)
A7: Oh my... well my professional background in terms of sheer years is largely that of a small-town family physician. I suspect that 20 years of patient care in fact finds its way into a good deal of whatever I represent. However, through sheer happenstance, I ended up in the [name of organisation] on their Council on Ethical and Judicial Affairs and developed a true love affair, appreciation for, and some understanding of the role, the importance and the development of ethical principles and frankly the hierarchy because there are in fact huge aspirational principles and then often explanatory pieces that say application to a particular situation X, Y or Z. That decade that I sat on and chaired that group clearly shaped a great deal of both my interests and my perceptions. I shared that table with a changing series of scholars, clinicians, truly giants in the profession in some instances, and so I've had an opportunity I think not from my own perspective but from sharing really challenging discussions which very often came down to "yes but what is the right thing to do?" And I found myself coming back to that question throughout the conversations with Helsinki. Certainly, that decade of ethics, which has then caused me a lifelong commitment, interest, value for... I'm sure was part of what drove me to go up and say we simply can't drop this conversation. But I've also spent ... I'm not sure I want to tell you how many years... over two decades how's that? In democratic physician organisations and recognise that the process in some ways is almost... almost as important, I think ethics trumps it but it certainly it has as big an impact in where you end up. And so we have to accept the fact that where you have a wide variety of people, and the [name of organisation] represents a huge variety of people but nothing compared to the World Medical Association where we're talking cultures, languages, generations, all sorts of things... that sometimes the process itself helps determine where you end up. So I think probably all of those pieces.
RC: Thank you very much. I can stop the tape there.
(END OF INTERVIEW)

INTERVIEW WITH MEDICAL RESEARCHER NO. 12 (MR12)

RC: This is an interview with [name of interviewee and organisation]. Thank you very much for agreeing to be interviewed today about the Declaration of Helsinki. I think to put this in context, the first thing I'd like to ask you is just to describe in brief terms your role with [name of organisation].
MR12: Right, my current is that I'm located within part of the global clinical operations group. Specifically in a department that works under the name of Medical Standards and Policy. And the routine activity of that department is to develop and maintain the necessary policy documents and procedural documents that effectively are the means by which the staff run clinical development programmes. And so these documents, in a sense, integrate external regulatory type requirements and other requirements and other relevant guidance documents such as, for example, the Declaration of Helsinki. The internal process documents integrate those relative to say the organisational structure of

[name of organisation] so that everything is meshed together in a way that allows people their various activities but such that particularly in the context of developing new medicines where the data are going to be part of a submission to regulatory agencies, all being well, that means that particularly in that circumstance not exclusively but particularly in that scenario all of the data and means by which the data were generated is potentially subject to compliance checks by the inspectorates of the regulatory agencies. And so my role is that, although I'm still partly involved in the development and maintenance process of how these documents are generated and then amended, updated etc. In the last couple of years, because of the amount of activity that has been going on externally, which potentially could impact that ... those types of documents, I've been spending more of my time trying to spot things coming rather than finding that things have happened externally and that any opportunity there might have been, firstly to be better prepared for it, and secondly if we didn't feel it made total sense, to try to influence it, in the past, not just in [name of organisation]and its legacy organisations but ... I think it's fair to say in industry at large in a number of these areas we weren't tracking that type of activity, partly because if we focus it on the Declaration of Helsinki as an example, until the early '90s or even the mid-90s, the Declaration of Helsinki, for the industry, had never had any contention around it. Industry was perfectly comfortable with it, totally supported it as being probably the single most appropriate reference to underpin the conduct of clinical studies and clinical research.

RC: Right, thank you so your...

MR12: So just to sort of come right up to the present, what I was finding that I was doing without it, as it were, being a formal of my role, in the last year or so, it has now been recognised that it wasn't just the Declaration of Helsinki activity that was needing to be monitored [but other legislation and guidelines]. A different type of process, and a different set of documentation but still very much going to be affecting how we operate and .,. Since the group that I'm part of has a global role, although we don't try to take it to the extent that we are absolutely on top of what's happening in every single country, at least for the major countries and the major markets from within the global group, we try to, as it were, keep a finger on the pulse. So it's working through colleagues in these other major countries in a sort of a matrix fashion. But at least we are able to have a global perspective and if we see that in one country they're perhaps thinking of going a certain direction in one area of regulation, we can probably bring to their attention that, "well that's been tried somewhere else and yes to a certain degree and it's practical but if you actually take it to the extent that you appear to be suggesting, we know from experience..." And so we would try to, if you like, broker, that's maybe formalising a bit too much, but we'd certainly try to give them...we try to give them the benefit of our insights on a wider geographical area.

RC: Right. So I've got your card in my office but what is your job title again?

MR12: Director, Medical Policy and Standards. And then I think probably it has in brackets 'external affairs' which is to designate and... so ... I would say that probably about 50 percent of my time now is spent ... and acknowledged within the organisation as being externally focused and about 50 percent is where I still make a contribution...

RC: You feed back?

MR12: Oh yes. That's the only reason it makes sense for them to let me spend 50 percent of my time tracking and engaging with these external activities. ... So in contrast to a lot of my colleagues who are in R&D or who are in clinical development, I've actually spent about half of my working life in sales, marketing, commercial roles. And then made a transi... well it wasn't a planned transition to get me into clinical development, that's just how it has worked that I transitioned from if you like front-line marketing through a central (10min36sec) new product development department which was sitting literally in between the R&D functions and the commercial divisions. And it was producing packages of information about potential new products that were coming out of R&D in a fashion that allowed the commercial entities to make an evaluation of them so that we could the decisions at an early stage is this something that we continue investing money in? Is this a product or an idea that looks as though it has marketable potential? And I was in that new product development though at a time when for our organisation then, the clinical development function was becoming much more subject to external regulation good clinical practice was becoming the norm. And although to a large

degree we practiced we practiced what was becoming formalised as GCP, nevertheless there were still new aspects of it that were having to be taken account of. And that factor, and also the fact that we transitioned out of short-term acute therapies into potentially long-term therapy areas such as cardiovascular disease, CNS-related diseases. It meant that the clinical development part of the entire product development cycle was becoming much more significant and in fact was often ending up as the rate-limiting factor. So there was a significant expansion of clinical development activity. And in the event, I mean the way that that happened to work out, I was asked by the then global head of clinical development if I would go into a role which was essentially operational support but with a particular short-term activity of aligning all of our procedures with the now formalised. Now things have moved ahead on that and the industry at large works usually within the framework of ICH GCP which is a more harmonised package of practices. So that's how I've got to be where I am but not the classical route actually.

RC: .... obviously quite an institutional memory would be being applied... Now I guess it's time to turn our attention to the document at hand. Before I take you to specific paragraphs of the Declaration of Helsinki that changed in the year 2000, I'll just outline the structure. I always come back to 2 key words if we seem to get stuck in the discussion: that's your experience of the impact of the changes in the 2000 revision and that includes your experience of the impact on the debate.

MR12: Right

RC: On practice and on the debate. And given that it's only 3 years that it's been in place, your opinion regarding the likely future impact of the changes. So experience and opinion. So really I guess at this point before I take you to specific paragraphs I just give you the opportunity to comment more generally on your experience and opinion regarding the 2000 revision.

MR12: I think before we got to the point of the 2000 revision, we have to acknowledge that there did seem to be a mind-set change somewhere in the WMA. And my personal suspicion is it was probably in the WMA headquarters operation or at the senior levels of the WMA management structure. Because leading up what became the 2000 version, there was an active part... an active attempt by the WMA to encourage and request comments and views on drafts that they actually put into the public domain. Now maybe it's because folks like me weren't sufficiently attuned to the prior processes, say in the '80s, or in the early '90s. And maybe that is what it was because we never had any reason to be concerned for taking a keen interest in what folks might have in mind to do as the next adjustment to the Declaration. But I mean you could almost characterise the situation in '80s and the early '90s that when there was ... and they were fairly infrequent... amendment to the Declaration, a typical practice in the industry is that as we write a specific study protocol, there are certain parts of these protocols that are generic, especially to do with administrative aspects. The bit that's not about the specific study design and the specific practices and requirements around this individual study. You'll find that they follow sort of a fairly standard pattern from one company's protocol to the next protocol etc. etc. And part of what is usually in that area of the protocol would be for example, references to certain standards that are going to be relevant to the study. And the Declaration of Helsinki was a virtually automatically referenced standard for the ethics, the standards of the ethics that we expected. So when they modified from time-to-time the Declaration we would simply take our old template and say, 'well it's not the '89 version anymore, it's the ninety-something, '96, whatever'. And we almost did that by rote. But certainly there were some companies who became aware that during the mid-90s there seemed to be a lot more obvious contention around the Declaration. And certainly that stimulated me to begin to take much more of an interest in it. It was facilitated for me I guess because at that point I was also actively involved with a GCP forum. ... It is a cross-sectoral organisation, contrary to what some people seem to think that it's an industry organisation. Sure, there are industry folks who are very active participants in it but it's not an industry thing like say Institute of Clinical Research here in [name of country]. It accepts into its membership and tries to actively encourage regulatory agencies, academic physicians, academic professional societies, patient consumer groups, it tries to be a forum as the name suggests for people who might have differing views on particular things related to medical research, clinical development to come together and see whether we can sort of help to reach or work towards consensus. Anyway, I was actively involved in that group and

primarily because of [name of another individual], who from his broader vantage point was taking a keen interest in the Declaration, I became aware that 'hey there's a lot going on with this. This next revision is not going to be perhaps as straightforward as the previous revisions'. And it was quite satisfying to see at a certain point that the WMA was providing opportunity for the wider stakeholder community to take an interest in what was going on. And they were able by that time to release it through their web-site. So they had a process that perhaps is more practical for them. (21min12sec) Because I think frankly until the early '90s, the Declaration as I perceive it anyway, was still essentially a Declaration developed by physicians for physicians. Although in reality I think this is what the WMA perhaps have only ... only appreciated in reasonably recent times whereas when it started in '64 the level of such industry-sponsored clinical trial activity and the complexity of clinical trial design was nothing like what it is at the moment. And in those very early versions of the Declarations it was fulfilling a need that was directed towards that physicians did the right thing by the patients which is the essence of it quite rightly. But because it was so good at what it set out to do, it achieved this ... some form of say gold standard, the profile of ... even cornerstone, or lynchpin or whatever phrase you would like to use, where everyone went back to when they had some dilemma around the ethics to do with biomedical research. But I don't think that the impact across the wider set of stakeholders was perhaps fully appreciated by the WMA until somewhere in the '90s. But at least they did begin to recognise it prior to the 2000 development exercise. But although there was a consultation, which I believe was really quite protracted because I think there was a sort of abortive version that was dumped, then there was a revised version ... and certainly industry made a lot of comments on that along with lots of other stakeholders and they then took that into the 2000 annual assembly and historically one of the things that I had noticed was that when they did make a change in the course of these earlier instances, I've not been tracking it, what we've tended to find was that somehow at some point which might even be months after the event, it would suddenly become known that 'hey, in '89 at the annual assembly they modified the Declaration and here we are in early '90 and we're perhaps still using the old version. And then we'd make that change to our templates and we'd start referencing the up-to-date one'. There was never any terribly visible process to the elements outside the WMA when they made these changes. And so knowing that they had to have this consultation exercise prior to the 2000, and that they then had a web-site, I was... we were not invited in any way that for example some of us were fortunate to be invited to the Helsinki meeting and I ... if there were any pharmaceutical industry folks at the 2000 meeting my suspicion was that it was because they were associate physician members of the WMA but I don't think that industry had been invited to observe as such. So literally on the Monday after their assembly finished, I thought it's probably too early but I'll go on the website and just see what's what and the new 2000 version was already there on the website. And I think they had taken the decision on either the Friday or the Saturday at the meeting in Edinburgh. (25min56sec) So it was instantaneous with no release note. There was no supporting document. It just sat there which in the sense of they'd made it visible - great. But to folks who'd been following the dialogue and the consultation, we couldn't make the link because the document that we understand had gone into the assembly as the draft was significantly different to what came out and what popped up on the website. So yes, prior to the 2000 version there was a clear change of attitude in acknowledging that they have to consult with the wider group of stakeholders but there wasn't anything like total transparency to anybody who had an interest in seeing what had actually happened. So unlike this occasion where I now know ... you know... what actually happened around the fact that it basically stalled at Helsinki and there wasn't a sufficient consensus to take it to any conclusion. I don't ... from any sort of direct observational I really still don't know precisely what happened at Edinburgh and maybe in the immediate period before where the group of 3 were finessing the changes. I also now, on the basis of what I believe is the procedural aspects of voting, had for example at Helsinki this year had there been a consensus that could have been recommended out of the ethics committee through council to the plenary session, it's my understanding that they need a fairly significant majority of the delegates who are entitled to be voting at that plenary session. And ...

RC: Yes I think its 75 percent.

MR12: It's 75 percent. And so they either got 75 percent or more vote at Edinburgh..
Anyway even if it was unanimous - because unanimity can be interpreted in two different... at least two different ways, in other words was it passive unanimity... or was it unanimity because everybody believed 100 percent that this really is what we must have. ... from an industry perspective in particular, I was very surprised and a bit alarmed by what we saw in the 2000 version. Fortunately we literally saw it at the beginning of the week after the assembly and as an organisation within about two weeks we had taken an initial view and we then began to ask our colleagues in other companies, and interestingly the views were pretty much the same but focused primarily on article 29 and 30.
RC: Well let's go to those. Here's 29 and remember experience of and opinion regarding and I've reproduced to help us the previous, the 1996 version. So I've started with 29 as it came out in the year 2000 and then look at the note of clarification and would you like to make any comment about...
MR12: The actual words are not so significantly different as a collection of words. But in the way that they were re-expressed, certainly our view and my personal view was that there was a firmer tone to the amended way that they had constructed that statement. But alongside that, and this certainly for me was as significant as the different way that they'd expressed the sentiment was that there, although it didn't appear as I recall on the WMA website, somewhere there was a press statement that was attributed to Delon Human and so in ... somewhere in the press shortly after the assembly there was a statement and sure, press statements as they end up in print are not always absolutely the way that they were perhaps intended by the person who made it available but essentially Delon Human was quoted as saying that the intent of this new statement in paragraph 29 is to pretty well eliminate placebo-controlled studies we don't think they're a good thing. And so I was looking at what was written but seeing this message from the secretary-general of the WMA saying what the WMA supposedly believed the intent and, if they were applied, the result ought to be. So it was the combination of the two ...
RC: Right.
MR12: That was really heightening concern around 29.
RC: Yes because many have looked at '96 and compared it to 2000 and have said 'why wasn't there the same fuss in '96, they seem so similar?'
MR12: I think if you recall what I was saying at the beginning of this discussion. If we had been as industry in particular, and maybe even also well I was going to say maybe even also the regulatory agencies but then I'm reminded that at least for the FDA, they don't still feel that '96 was...
RC: Yes they didn't update...
MR12: ...was a vintage edition and that their formal position, they reference it back to '89. So from the industry's perspective, I think if we'd been paying as much attention in '94, '95 or whatever period led up to the '96 change, maybe we would have started that dialogue a bit sooner. But essentially we were still taking the Declaration on trust up to the '96 version. (33min57sec) And so the fact that they saw fit to make a change which they then said in public statements was to make it clearer that placebo-controlled studies really should not be done, in circumstances where there are alternatives.
RC: And yet interestingly the '89 version differs only from the '96 in the 2nd sentence which specifies placebo. It still, some have said, calls into question placebo because it said 'should be assured of the best proven method'. And that was in the '89 version. So some have said that...
MR12: Yes.
RC: Placebo was still in trouble even when...
MR12: You can dissect these statements whether it's 29 or 30 or some of the other ones as well, if you actually really put them under a magnifying glass and dissect it phrase by phrase, word by word, there are actually lots of bits all of us in some way would have a personal view as to how it could be more clearly expressed.
RC: I see.
MR12: And you know if I draw an analogy with say some of our internal policy documents, there's always a problem writing a policy document by committee. Because at the end of the exercise if it's truly been done by a group of people who aren't absolutely unanimous then there are always tensions

and you end up with verbage which seems to satisfy the most common ground that you can identify but no-one's totally happy with it. And ... we have to recognise that that's almost inevitably the case with the Declaration of Helsinki as with lots of other documents. But the other ... the other factor was that clearly this whole issue of the extent to which placebo-controlled studies should continue to be regarded as acceptable with the extent of the wider extent of discussion prior to the 2000 assembly meeting, it had sensitised at least some ethicists and therefore ethics committees such that very shortly after this appeared we were beginning to be challenged where we put forward protocols that did involve a placebo whereas up to that point that ... to any significant degree had never been the case before. So therefore it certainly produced a sort of a environmental change in the broader thinking of some of these groups. Now that's not to say that they were necessarily looking at it and sort of coming at it with a full understanding of all of the different aspects even now there are ethics committees who will challenge issues that they think they're seeing in protocols on the grounds that this doesn't seem to be totally in alignment with the Declaration of Helsinki. They're doing it in some instances simply because it's more of a sort of ... I would say it's more of a checklist mentality than a real deep thought process about the fundamentals of what this is all about.

RC: Some would...

MR12: And the reason I think that that's at least in my experience can be said is that there are quite a lot of instances since 2000 where ... I mean not that we have these challenges, if that's the right word for them, even say on a weekly basis the frequency is much less than that but the standard sort of challenge we get, given that we still in our protocols reference '96, we don't ... we've not formally referenced 2000 or it should really now be 2002...

RC: Yeah, although they don't list that as a full amendment. In the preamble, if you look preamble now it still says 'amended', 'amended'... and then its got in brackets (note of clarification added) so they don't call it an amendment.

MR12: I had thought that now if you go onto the website you will find that there's another line below Edinburgh which says...

RC: 'Note of clarification added', it doesn't describe it as an amendment.

MR12: Oh sorry, it's not being amended but if you then actually go to the document and there is only one version now resides on the publicly accessible web-site, the document in total is as published in 2000 and the note of clarification is formally added in the same... now in the interim from 2001 when they took the initial ... technically it isn't an amended article ... but sorry coming back though to the issue of where we have sometimes challenged in the period from 2000 ... the typical challenge is why I'm referencing the 2000 version, it's not usually made in the 1st instance with reference to either (40min54sec) 29 or 30 or any other. In other words the challenge is hardly ever expressed in terms of a specific concern that's legitimate to the protocol. And in most instances when we're asked the question why are you using the 2000 the study design is such and the conduct of the study is such that 29 and 30 are actually non-issues in any case.

RC: Well if it's a phase I trial then...

MR12: Right. In these protocols. Nevertheless there are ethics committees who are obviously aware that there is a later version than '96 and so they are asking the question. And most of the times we then go back to them and say 'well the reason we're not referencing is the following... and in any case in this particular study the points that are still in contention and still the subject...'

RC: What reasons do you give for not referencing 2000?

MR12: Well the primary reason now is article 30 and the fact that potentially it could be construed and we know that there are some ethics committees, and we know from the debate in Helsinki that there are individuals certainly who see... who feel that article 30 creates an opportunity to insist on continuity of medication at the end of a study. And we're not saying that in all instances that that's not a legitimate stance to take because we currently would do it in the most obvious instances but it's the fact that there's a looseness about the wording of 30 which if folks who feel they may be able to control how many protocols are implemented and particularly what then should happen after individuals cease to be actively participating in the study, it does open the door to them to try to derive more from paragraph 30 than we would feel is always justified.

RC: We'll come back to that when we've got paragraph 30 in front of us. Can I get you to make any comments you'd like to make on the note of clarification?
MR12: Well just that the note of clarification is again, like other bits of the Declaration, it's not perfect. There are aspects of it which could also have been better expressed but at least it recognised the two key concerns that I think were concerning regulatory agencies as well as the industry. And to that extent we are reasonably comfortable with that. We feel we can live with 29 as it's now supported by the note of clarification. If at some point they feel minded to try to integrate the concepts of 29 and the note of clarification and if someone can come up with a way of integrating it without writing a whole essay around so that it can all just become an amended 29 then great. I mean I'm sensitive and I personally support the idea that we shouldn't see 29 ... or rather we shouldn't see the note of clarification to 29 as creating any sort of license to add notes of clarification ad infinitum because I do think that's an essay.
RC: There's so many questions now that I'd like to ask. I'm conscious of time, but perhaps we could just pause on 29 a little bit longer. The word 'or' as the connector between the two clauses scientifically sound methodological reasons 'or' it's a minor condition with no... this has been challenged that it should be 'and'. Any thoughts on that?
MR12: Yes. (45min37sec) My personal view would be that it's perfectly fine as it is but I can understand that if you're coming at it from a purely ethics perspective then clearly it's tighter and coming at it from the perspective of trying to ... of the sort of the... the firmest and the best ... I suppose it's the most restrictive criteria from a patient perspective, clearly then you put 'and' instead of 'or'. But the sense I sometimes is that a lot of the discussion and debate about this is in a relatively abstract conceptual sense. And at least in terms of that part of the activity that it covers that relates to what our typical work is, there has to be a balance between, if you like, what might be the pure ethical approach and something that's at least recognising there has to be some pragmatism. And many times in the debate I don't get the sense that and maybe it's because we've not educated some of the folks, some of the other stakeholders maybe we've not educated them enough so that they understand what some of the practicalities are.
RC: I think the argument that she made, and it would be interesting to hear your response, was that if you did have someone who wanted to push the meaning of that as far as they could, and said 'well this study, we think we've come up with a methodologically compelling reason to do this. We acknowledge that this may irreversibly harm some of the people that were on placebo but it does say or, and we have fulfilled one of the criteria and so we do seem to be compliance with the Declaration of Helsinki as it's been clarified'.
MR12: Right but that though is also appearing to ignore the role of ethics committees in the way that studies have to be vetted. We're not able or entitled to simply reference an interpretation that we may make of what we feel could be considered legitimate under the Declaration of Helsinki and say 'so that's our interpretation, we think that we are in the clear in the way that we are interpreting the Declaration of Helsinki therefore we are going to start this study tomorrow'. That's exactly what ethics committees are there to do. And an ethics committee whether it's with reference to the Declaration of Helsinki or some other document or just their own perception, they can simply say 'we're not granting a favourable opinion to this study'. And at that point in time, that's then dead in the water.
RC: Because of other clauses that require you to assess the risks and burdens and that sort of thing.
MR12: Well just simply on the grounds that ethics committees are entitled to express their opinion...
RC: But hopefully they're reading...
MR12: Yes, they are, but whether they're using this as their frame of reference or whether they are not and just taking a collective view around the table, if they decide that they're uncomfortable with it, and that they're not happy with it going ahead then certainly in our case, we're not going to proceed with that study.
RC: No I guess what I was wanting to go back to was your original comment that that seems to be interpreting in complete isolation paragraph 29 whereas if you look at rest of the Declaration there are

plenty of places where it says you must assess the foreseeable risks and benefits and if someone came with that as a justification for potentially doing harm to the placebo group, you could throw it out on the basis of plenty of other clauses and so... I guess that's wanted to see if that is what you're saying.
MR12: And I'm not sure if that isn't perhaps touching on someone else which I felt seemed to be a hardening of sentiment for the 2000 document as a whole. Somewhere in the document there is a piece of text that talks about the Declaration should be considered to be ... nothing in national law etc. etc.
RC: We'll come to that later.
MR12: And so we have this very responsible, well-regarded organisation trying to put forward the view that ... this comes before national law is one way that you can interpret that. Now that also, as I saw it, was quite a significant change. And again I'd have been very interested been able to hear the debate, or been able to understand the debate if there was a debate which prompted them to move from where they'd previously been to ...
RC: I mean we could come back to that ... if that's okay. I guess I've got one last question, we're taking a lot of time on 29...
MR12: Sorry.
RC: No no it's understandable because obviously you're ... you know ... you're giving a pharmaceutical industry perspective and these are major issues that face you. Some challenge and I'll put it as a very general challenge; if there is an active treatment, why do a placebo-controlled trial because surely you want to prove that your compound is better than what's there for the patients not that it's better than an inert compound.
MR12: Well ideally yes we would but methodologically, especially if ... because by better, can I assume that you're perhaps thinking from an efficacy standpoint...
RC: Efficacy, even side effect profile...
MR12: Well, right but generally when people put this point they mean if there's something else and you probably would wish to show that yours was better, the first take is usually from an efficacy standpoint.
RC: Yes I suppose because if it doesn't work why would you worry about...
MR12: And this is where methodologically it then has other consequences because the numbers that are almost inevitably going to be needed to have the statistical power to prove whether you truly are better or not on efficacy characteristics are going to be expanded very very significantly. Now I'm not a statistician and I sort of can't quote examples and the scale of difference but you know it's there, it's in the literature. And Bob Temple is one of the proponents of this point. And so the thing can go full circle in the sense that you could be saying 'right if for the sake of argument the difference was between doing a 400 patient study to prove equivalence, as opposed to doing a 4000 patient study because that's what you would need if you were going to have any chance statistically to demonstrate superiority then there's an ethical dimension to that as well because you're working then with a 10-fold increase in the number of people who are participating in a medical experiment. And if in a particular scenario it may not always be the case but if you had a particular scenario where one of the motivations to take this potential product if that's what it is further is because it's considered that the side effect profile is better, then why have 10 times as many patients providing obviously that to have the proper data that would support any conclusion around side effect profiles, that you've also got an adequate number.
RC: Thank you. Of course the ethicists then come back and say 'well the problem is, if it's your patient, even if there's only 400 others instead of 4000 others, if it's your patient, you still need to worry about whether they'll be harmed being on a placebo' so how does...
MR12: So then is the Declaration saying that the broader societal considerations should never have any place in this ...
RC: It does say that the well-being of the human subject should take preference over the interests of science and society. And that obviously comes out of the Nuremberg original and obviously those horrific trials. We learned a lot about hypothermia and things like that... I mean again how do you fit that in when you are writing your policy.

MR12: We would certainly take a view that we would need to be balancing and sort of integrating the broader perspective to a greater extent than the words in the Declaration would appear to suggest. (57min31sec) And I think some of our support for taking that view is that regulatory processes which are government-driven in all the different countries require that we do studies in a certain way to generate a body of data without which they're going to provide licenses. So there is a tension...
RC: There is a tension and I think you've articulated the tension you know even the guardianship role of ethics committees extremely well and that's very interesting. Thank you that's extremely useful comment. And just make sure there's nothing else...oh yes the last question where you are not using a placebo and you are doing much more of a head-to-head trial. Some have argued over the interpretation of "testing the risks, burdens, benefits etc. of a new method against the best current method". How do take that? Is it the best current in the world? The best current in the U.K. which is sometimes not as good as maybe what they're offering in the U.S.? Or if you are doing a trial say in eastern Europe, is it the best currently available in that country or the best in Europe or how do you...
MR12: Well essentially that's one of the most problematic phrases in the Declaration at the moment. Because it's a well-intentioned phrase which almost defies application. There is seldom at a global level such a thing as the best... whatever which is the
RC: It just says best current?
MR12: The best current. And even within the ... what one country's health practice medical practice there may not be unanimity of view. So when we are doing comparative trials, depending on the geographical coverage of the trial in other words if it was a trial that was only happening in the [name of country] then we would be looking to use the other recognised standard treatments generally ... the currently used standard treatments to the best consensus view that we could. And to that extent that's one of the roles, not the only one, but it's one of the roles that can be played by some of the advisory bodies ... or advisory committees that we put together to provide an external expert view around study design for example. But then if you extend the situation, as we increasingly have to these days, to get the relevant scale of studies and marrying the scale that's needed against a time frame we end up quite often using a collection of different countries and then, of course, you get the problem being compounded because you have to, for study design purposes, you clearly want a common comparator, and so ... and sometimes you do have to adjust the mix of countries because you could have a situation where for various reasons there could be countries where they have the therapeutic experience and they have the investigators who would be well-able to do the study but for some reason the comparator you have available that is recognised as being relevant to most of the other countries hasn't yet made it onto their market. And so you sometimes have to say "yes we would have liked to have included your country, but since you don't have product X and we feel it's critical to this particular study, you can't participate".
RC: Thank you that gives a very useful practical example of how the interpretation can get very complicated.
MR12: I mean, without being too specific I can quote you another example which is probably at the other end of that spectrum where there is a potential product sort of at the middle part of its development, its pre-clinical development programme where there's only one other similar type of product already made it to the market. And that has only been at this point in one country. And so if the decision is taken that it's scientifically and medically relevant to conduct a comparison as part of the pre-registration programme with that product, there's only one country we can go to do the study at this point in time.
RC: And practically is... well I think we better close the discussion on paragraph 29 those are superb examples though. Paragraph 30, the other major bone of contention. Your experience of the impact of this on either the conduct of research or on the debate regarding it or your opinion regarding the likely future impact.
MR12: Well, in a nutshell, the views not just of [name of organisation] but broadly of the industry here is that this is potentially opening up to those who wish to interpret and try to apply it in such a fashion, it's opening up the possibility that it could be seen as a mandate that the sponsor, whoever the sponsor organisation is deemed to be, has an obligation either to provide continuity of the study where

it's considered by the relevant parties to make sense, or if not the study drug, perhaps the local standard of care for patients who've participated. And it's written in such a fashion that it doesn't specifically say this has a particular relevance in life-threatening diseases or in diseases where patients would be put at a particular disadvantage if literally then nothing was following on. But interestingly just going back to the immediate sort-of aftermath of the 2000 version being made public. One of the very first challenges we had from an ethics committee within about 3 months of the 2000 version having been issued, and it came not so much as a challenge but it came framed as an enquiry will you be continuing to provide treatment to these individuals after the end of the study? So the very first instance of that being raised to us by an ethics committee wasn't from the parts of the world where you could have envisaged that it might have been considered to be more relevant where there was no health care infrastructure, this was actually a question being asked from the [named country] where in a disease area such as cardiovascular treatments, to a very large extent, even though we think that we've got potentially better ones, there isn't a shortage. And there's a health care system that will deliver another very adequate therapy to patients who've completed a period on a potential new product. So that's I mean and we shouldn't make too much in a [name of country] context anyway was a relatively isolated incident and it may simply have been that it was prompted by the fact that there had been discussion arising from the process of getting to the paragraph 30 wording.
RC: Some have said, and it... I'm not raising this by any means to be a journalistic style where I confront you on that... it's really to explore the issues so that we ... it is then important to know what people are arguing on the other side of that coin. Well why not? What is wrong with some kind of obligation on the part of the researchers at the end of the trial? Or if means providing someone with an antiretroviral or an antihistamine for life those people put their well-being on the line that will make your product that will hopefully earn you a good sum of money? And this is especially so in situations where and they are across the spectrum you've gone into say a poorer country, provided treatment for people who wouldn't have access to it otherwise and then are leaving at the end of the study? And that there's no infrastructure to help them? But it also may apply in a situation where the antihistamine - to use the example - is in the [name of country] but it's not going to be funded under the formularies of the local health boards? But it was really good it's just too expensive but these patients who helped you develop did very well on it why not you know give them a supply of it? Maybe I just throw that to you... there is a barb in that particular issue too which we'll come to later but I'll put it to you as a pharmaceutical...
MR12: There are a number of very practical considerations. It's assumed ... or the wording certainly does nothing to differentiate where you might be in the evolution of this product. (68min47sec) And certainly for quite a significant part of the clinical development programme, there is no absolute guarantee that this product is going to generate a body of data that will be considered sufficiently adequate... and not just clinical data but the pre-clinical data as well, some of which will still be continuing in parallel when the clinical development programme is running. And unless the entire package of data substantiates, or is considered sufficient to substantiate licensing the product it may not even ever be licensed.
RC: Some have said that doesn't really raise a problem here because this is a guiding principle and the idea would be "okay if you the product never gets a licence then it's not an issue because you can't provide it to them".
MR12: Right, so let's then take the situation where in a phase II study there is an individual who seems to be getting benefit which in the opinion of their physician was more suited to them than what they'd previously been on. Should they have been allowed to continue for whatever that period of time might be until the licensing authority had either said "we don't think there's enough data here to justify this" or if we have taken that view beforehand. So there could have been 6 months, 12 months, 24 months of additional treatment. And if one of the reasons why, at the end of the exercise this wasn't concerned was actually more to do with potential toxicology, who is doing whom a favour here? (70min38sec)
RC: No that's an extremely good point and others bring that out as well and I just wanted to raise that...

MR12: And so there a simplicity about this ... and I'm sure you either done it yourself or you've heard others sort of go through... you can dissect almost every single phrase and in some scenario or other there is at least one potential problem with each of the bits. You know "at the conclusion of the study..." which in some people's minds is saying "so if they finished the study yesterday then from today whatever today might be and wherever that fits in this other timeline of events and activities, this is what should be happening to me". And "every patient entered into the study..." - but only half of them have perhaps been on the ... so what's that bit saying?
RC: Well I presume what that bit says is for example, you're trialling a vaccine and you put half on a placebo and half on the vaccine and you find it's very good then you actually give the vaccine at the end of the study to the people who were on the placebo arm to give them the protection as well ...
MR12: Fine and that's an example where you can sort of square... well not square the circle but where there's a logic. But where if we go back to the antihistamine case so we've got potential new antihistamine against potential existing antihistamine and every patient entered into the study should be assured of access to the best proven identified by the study and the view at that time is that the best proven looks as though it's the new product...
RC: Presumably then people would argue well there may be some kind of moral obligation to at least give the placebo group the opportunity to see if they can benefit because they did after all provide the evidence for you... but I don't know how you'd respond to that...
MR12: Well I think in areas where both from a geographic perspective and other available therapies and health care infrastructure where well-proven existing therapy is available then I think there are counter-arguments from an ethical perspective to not extend the experimental treatment longer...
RC: Presumably primarily about concerns regarding establish safety data.
MR12: Yeah.
RC: Can I put two other things to you which I think it would be very interesting to hear your viewpoint on this. One or two commentators have said one of the problems they say with paragraph 30 is it really puts the pharmaceutical industry in the box seat as far as researchers are concerned. Because if there is an obligation at the end of a study, they're the only ones that are usually developing a product for profit and so they may be the only ones that have the wherewithal to do studies in places like sub-Saharan if there is an ongoing responsibility. The funding bodies would never be able to do that, the universities, academics would never be able to do that and so how do you respond to that as a...
MR12: That we might be the only...
RC: The criticism was that this is too much favouring the pharmaceutical industry and at the exclusion of the academic sector and others because potentially they would be the only ones who could really afford to meet the requirements that appear to be...
MR12: Well I can fully understand the point they're making. (74min30sec) because they're looking at it in terms of sort of the economic viability and that, for them, it's just totally unfeasible. Whereas the industry, if it really put its mind to it, has considerably more resources that, if it took the view that this was worth doing... but in reality and admittedly it's not always been the case but I think for the vast majority of the responsible research-based industry at this point there is now a lot more internal consideration and discussion and thought goes into the extent to which we should be going to non-traditional countries unless the work is compatible with the perceived health needs of the country. And in order to make that judgment, that even if we felt we had the contacts and the resource to take our own decisions in that sort of scenario, we would now be much more anxious to involve the local Ministry of Health, the local regulatory agency, the recognised ethics experts from that country or that locality as part of the process of determining whether an activity of that type should really take place wherever. And we have a back-seat business and we are quite well used to recognising that at the end of a study, it is not acceptable to collect up the case report forms and the other bits and pieces and just lock away and that's it. But it quite often does have to be something that's applicable, extended and that.
RC: Some would say that this is taking the principle that patients shouldn't be worse off after the study than they were during the study. So if they did well during the study and they're on

antiretrovirals they should be then left without them at the end. And others say "well really what this is doing is just making researchers... doctors... people, participants aware that they need ethically to think about the fate of their trial participants after the study and that what the requirement should be is that this is spelled out beforehand and negotiated beforehand. Would that satisfy the...
MR12: Absolutely. Absolutely. If the intent, as you expressed it at the beginning of your statement, if that was the real intent that was meant to come through from 30 then don't write it in such loose fashion that it's capable for at least the industry to see the potential problems that they could be faced with from people who try to utilise the full flexibility that's in this loose wording. (78min04sec) State what the objective is in a way similar to how you expressed it because that ... I don't think there would be any issue with that. In fact, I think if you go back and look at some of the suggestions or key elements of some of the suggestions that were made either to replace or to complement 30, that's part of what you will find there. That is let's be open about this declare what the plan is in the protocol, that's not to say that if someone feels they can justify it, that the plan may still say "we run the study and there's minimal continuity thereafter".
RC: You'd have to get that through the ethics committee and get consent in that context.
MR12: Yes, exactly. So I think this is rather poor wording that's actually trying to reach or might be trying to reach an endpoint which I think we would have no problem with.
RC: Well, thank you. We've used our planned time. I don' t know if you've got 10 minutes to run through quickly I guess we do need just brief statements. Paragraph 19: now this is back in the part of the document that applies to all research whereas these two were research and clinical care; reasonable likelihood of benefit to the populations. You've already alluded to the use of non-traditional countries and that sort of thing...
MR12: Well certainly this is now something that is much more in the minds of sponsoring companies that there has to be ... that there has to be a compatibility between proposed programmes and the perceived and... locally perceived needs that ... just because it might be an opportunity is no longer a good enough reason for...
RC: Okay, just the one now 27, that now requires... I mean there's an increased requirement for stating conflict of interest and reporting those but the middle sentence is completely new and that is that negative as well as positive results should be published or otherwise publicly available. Again, from a pharmaceutical industry perspective your experience of or opinion regarding this?
MR12: There is an increasing recognition that there has to be more transparency around the outcomes of studies. There has to though be a recognition also I think among some of the individuals and some of the groups who tend to present this as all or nothing that the nature of a study... that there are all sorts of studies and not just meaning the ones run... or sponsored by the industry. But not all studies are what might be conceived of as sort of the classical comparison of new product against existing established product. There are lots of studies that, for example, are purely methodological particularly relevant to the early stages of clinical programmes. And where from a patient perspective the outcome and the conclusions of these studies have really got no applicability for treatments that a physician could apply to his ... to his patients and some of those studies because of the methodological exploration that's being done, in some instances they are actually we would consider quite proprietary.
RC: So that you would have intellectual property rights over them.
MR12: So there has to be a recognition, I think, that it's not a what's the phrase these days a "one size fits all". But the principle that where there is... where someone has thought that this was a study worth doing and that this has clinical conclusions that may be derived then that has to be made available. (83min19sec) The question then is and fortunately we are in an age when there are more options than just the [named journals] type publication because frankly if this is going to happen, there are not enough publications, at least not the ones that would be deemed as being reputable, peer-reviewed etc. etc. And certainly even if you took all of the different types of journals that publish data at this point, they are not going to be falling over themselves to pick up the negative stuff. So as long as there is a recognition and an acceptance that sometimes this will be achieved through non-traditional communication processes and web-enabled and ...

RC: Registers of clinical trials, yes. Can I just come back to the proprietary issue because I guess that is where the conflict is likely to occur between anyone who sees the intent of this and your worries. A Phase I trial: you've got a candidate molecule phase I trial unfortunately something about it, it's pharmacokinetic profile it's not getting to where it should get, or it's a little bit more toxic than (84min40sec) than you know causes a bit more nausea... the patients don't like it, whatever. But you've got other candidates that you like and you don't want to publish this because it's seen as proprietary information. Now others might say now wait a minute, if people felt sick while they were on it, if it was a toxicity issue then it has to be published so that no-one else does this.
MR12: The chances are that in that type of scenario the only people who would have access to that particular compound might be us...
RC: What about somebody who might serendipitously might be working on something and that chemical attachment to the steroid ring has shown to provide unexpected harm and...
MR12: Well that could be a ...
RC: That where the issues rub...
MR12: That could be.
RC: I mean I don't see any easy resolution there I just want to make sure I understand the point. Well can I take you to paragraph 1 and this may have implications as well, the 2nd sentence being new. Medical research involving human subjects now explicitly stated to include research on identifiable human material or identifiable data. Any issues relating to that?
MR12: Well it will all hinge on interpretation.
RC: Where are the interpretation issues?
MR12: Well as soon as you use the word identifiable because culturally from a data confidentiality data protection perspective, there are totally different interpretations of 'identifiable' even between say the [two geographical areas]. So again, and I don't know if those nuances were recognised and the view was that that's not relevant to construction of this particular concept but I've... I guess one of the things that has prompted the inclusion of that was probably the Icelandic Decode...
RC: The Icelandic?
MR12: Decode was the name of the organisation that was doing all of that genetic...
RC: That's certainly been mentioned.
MR12: ... database.
RC: The other thing that's been mentioned in the pharmaceutical context is the storage of samples for later pharmacogenetic studies.
MR12: Right now that's an area that's very topical as you seem to be aware. And lots of people, not just in the industry, but in organisations such as for example CIOMS are putting a lot of effort into trying to understand what the real issues are around that. But again, it's not as simple as some people might think it is because in contrast and I'm not in any way an expert in this area so I'm trying to reflect what I hear other folks debate. The contrast is that if you take the typical samples for clinical chemistry, you run the assays, you get the result virtually end of story. You know you've got straightforward interpretations that will then be able to be made as to whether that's good, bad or indifferent. With the evolving pharmacogenetic area, it all seems to hinge on certain markers and although we... if a protocol was collecting samples, there would be in the short term some specific purpose that had been identified as being what they would immediately wish to use these samples to ... to assess. But the nature of pharmacogenetics is such that when, say at a later point in the programme, and perhaps using or taking a view across not just that particular study but a whole set of studies where you've got aggregate data, you may see something which may either be to do with efficacy responses or it could be to do with side effect profiles. And where it's then obvious to those who understand these things that in the samples that we took, if we still have them, we can now formulate a different analytical interrogation that we can apply against those samples which may help to elucidate why these patients are either responding far better or
RC: ...intolerant...
MR12: or this 20 percent of the population are having particular problems with side effects. And so that's why there is a reluctance to say "well we can identify right now that we want to do this test and

when we've done the test we agree that we should then throw them all in the bin". On the other hand there is a sensitivity because in some folks' minds a sample which has been taken although physically it is in all senses identical to the sample that you may have taken for more classical investigations, the fact that it's potentially now going to be analysed under a sort of genetic type umbrella raises sensitivities. And I'm not convinced that all of those sensitivities are entirely logical and legitimate. They're there. And it's because they're there that there is so much effort at the moment going in to trying to collect thoughts around these. And I think it's a major area for mutual exchange and hopefully sort of education to try to find a way through this.
RC: Well thank you. I think again in the interests of time moving along you've mentioned this one already. Any further remarks about paragraph 9 the revised way the document itself phrases its own authority? (91min49sec)
MR12: Just that it struck me as being somewhat high-handed. But then you can take the view that well although the WMA is an important body, and although the Declaration of Helsinki has a very high profile status in terms of biomedical ethics, it is only a document that's issued by a global professional body. In the absolute legal sense it has no status. So what shouldn't they try to carve out as broad a pitch for themselves as they possibly can?
RC: How it's often phrased, and it would be interesting in your... is that it's aimed primarily at developing... or very rapidly changing parts of the Eastern Europe, like you know Africa, Latin America, where maybe there isn't as stringent an ethical framework for approval of studies. And so what it is doing is that it's giving the doctors in those countries is a basic set of minimums. It's fine if your local system goes further no issue but if there is either legislative... there isn't legislative protection, or there's legislation that actually removes protections that the standard of the profession...
MR12: But again there's almost a language consideration to this. That sentiment which I know you can say that's essentially what this boils down to, but that sentiment could have been expressed in words more akin to how you've just expressed it and it wouldn't create the impression that they're trying to give an even increased status to the Declaration.
RC: Thank you, that's a valuable observation. The last specific paragraph, paragraph 6 and again in the interests of time what I really ... this is an expanded requirement to undertake research the specific is looking at those 4 criteria by which new methods should be evaluated is there any comment you would like to make on the choice of the 4 criteria I've cut this one a bit short in the interests of time.
MR12: The effectiveness, efficacy, accessibility and ...
RC: Sorry effectiveness, efficiency...
MR12: Sorry... efficiency, accessibility and quality. (94min28sec) It's not one of the pieces that personally I have the same sort of issues over ... feel that it's creating significant issues from our perspective.
RC: No, I mean some have questioned the word accessibility as to what did that involve people doing. The other that has come up is why isn't safety in that list?
MR12: Well it's not there as a word but again you see, do they think it's there embodied in efficiency?
RC: In quality?
MR12: What... quality of what? Quality of product or quality of benefit to the recipients of the medication? Again, as I said at one point, if you put all of these articles under a magnifying glass, I mean I'm sure that there are probably other issues in there that we've never even got to yet because we've ... the obvious ones have...
RC: In some ways, putting it to you as someone who's involved in an industry that's doing research, it's not so much an issue but sometimes you put it before an ethicist who's advocating a lot of more restrictiveness in some ways and then they're saying "hey wait a minute what about the ethical obligation to do research?" So in many ways I'm not surprised you don't have too much of an issue with that but it's there just for completeness.

The document's been restructured. Previously it used to divide research into therapeutic and non-therapeutic. Now it has basic principles applying to all medical research and then a subsection where medical research is combined with clinical care. Again, any comments about the restructuring?
MR12: I think in each case there were pros and cons. But the structure of it is not something I perceive as a major...
RC: It's not become less helpful because there isn't ... when you're in a phase I there's this nice separate section...
MR12: Well if I was somebody who was focused on phase I, then might have been the sort of response that you would have got...
RC: Whereas others have said "thank goodness it's gone, because we used to spend ages trying to decide is this a therapeutic or non-therapeutic study before we knew what the Declaration of Helsinki said about it".
MR12: And so as I say there are pros and cons. I think perhaps the ... again, it was a surprise if you like, at the point of transition. Oh this isn't what we used to recognise just from a structural point-of-view but well... we're three years in...
RC: The last one... I've obviously taken you to specific paragraphs. Now that we've finished that process, any other comments regarding the Declaration you'd like to make and then I have one last question and we're done.
MR12: I think the only general comment I'd like to make is I hope the increased openness and the partly increased transparency around the process on the part of the WMA continues because it may have started off as a Declaration written by physicians for physicians but in reality although they're still perfectly entitled to retain the ownership of it indeed the custodians of it, I think they do need to recognise that it has influence across a much larger group of stakeholders who aren't within their membership in the normal workings of the WMA. And if they continue down that track then hopefully we can work through these.
RC: Thank you very much. Now I said there would be one last question (98min49sec) and this is just as I go through this and interpret to help me to understand comments further. You've already answered this I think right at the start with the introduction to some extent and it's really a moment's personal reflection, a moment's self-reflection: how is it that you personally think that you have come to hold the views that you've expressed on the tape?
MR12: Well firstly from being within the pharmaceutical industry. And so to that extent, if there is a bias, then no doubt it would be towards the perceived thinking of the industry. But it's at the ... it's at the very practical level of these are the words in the Declaration but this is the situation in terms of setting up and trying to conduct a clinical programme. And what does this paragraph and the way that other people who have an influence on the conduct of our programme interpret it... is this all going to mesh together or is it going to produce conflicts and contention?
RC: Thank you very much. I will stop the tape there. We have gone over time but the comments you were making about placebo and paragraph 30 were so relevant and interesting that I think that was from my point-of-view justified – I hope it's not too inconvenient.
(END OF INTERVIEW)

INTERVIEW WITH EXPERT COMMENTATOR NO. 12 (EC12)

RC: I'm very grateful that you've taken the time to participate in this interview looking at the Edinburgh revision to the Declaration of Helsinki. Before I start I wonder if you'd be able to just look at the revision ...
EC12: Vision?
RC: Sorry – revision ...
EC12: Revision, yeah yeah.
RC: Amendment... although [name of another interviewee] told me off for calling it an amendment, saying it's a "revision" so...
EC12: (laughs)

RC: So... the ... I digress. Before I start however, I would appreciate if could just, so that I have the details right, explain your role with the [name of organisation] and any other sort of ethics fora or involvement in this kind of...
EC12: So I am currently the [specific job title] for the [name of organisation] and that requires basically making sure that the organisation functions in a decent way. And they have to make sure that I have to function in a decent way which is probably a bigger challenge. But the ... basically we're involved in looking at the ethical and scientific issues that arise in the context of biomedical or health research in [geographical area – multi-national]. ... It's an NGO, it's not a government organisation. It's an independent organisation which is very important to it. And for me it's very important to have that kind of platform.
RC: I mean I have specific parts of the text of the Declaration of Helsinki that I will take you too.
EC12: I just want to say also that I'm working also with this project [name of project] which has established fora for ethics committees in [various parts of the world].
RC: So an administrative and consultancy role?
EC12: Yeah, I ... they asked me to organise. I originally tried to do this myself in [geographical region], in 1999 they asked me to organise a meeting in [specific place]. And that's where they accepted the idea of having a forum for ethics committees in that region.
RC: Thank you. Okay going to the Declaration of Helsinki.
EC12: Right
RC: Edinburgh (2000) version. I'm interested in the impact of that. And that's both on practice and also on opinion(5min01sec) and the debate and also your opinion regarding what the future might be. So as we go to each paragraph I'll keep coming back to those ideas.
EC12: Good
RC: And any comment that you want to make on the text itself and it's interpretation.
EC12: Okay fine.
RC: So it's a fairly broad remit, you just go to the text...
EC12: And what's your objective in this study...
RC: In this study well I guess I'm looking at the impact of the Edinburgh 2000 revision the title of my thesis is "The Declaration of Helsinki and the Landscape of Medical Research" using that metaphorically
EC12: Right
RC: To see how... you know when the Declaration of Helsinki shines across the landscape if you like what shows up. And I'm looking at it from 3 points of view ... I'll stop the tape while I explain the objectives... Once again thank you for agreeing to be interviewed and before I take you to specific paragraphs I invite general comment about the impact of the revision in 2000. Anything you would like to...
EC12: I think myself the impact of the revision of 2000 is fantastic. It's enormous it's large. The text has really become the focal point for discussion. That's what I said... actually that's what I said yesterday in my talk. You know, Delon Human is right, it has demonstrated itself as the cornerstone of medical research. It's not really too questionable if that's the case or not. I can imagine people could question but I don't think anybody here anyway is questioning that. And I think the impact, because of this, is brilliant.
RC: Thank you. Any particular aspects of it that you would like to comment before we go to specific paragraphs?
EC12: No because the text as a whole remains...
RC: Now I'll take you to paragraph 29 which, of course I've reprinted the '96 version here's the original 29 with the Note of Clarification: now from the perspective of your experience of the impact of this or your opinion regarding the likely future impact of this, would you be prepared to comment? (7min25sec)
EC12: They're both ... That's fine. No problem.
RC: The ... some of the debates of course, have centred around issues like "best current" and what does that mean. The comparator arm required to be the best current. Would you care to...

EC12: Best current, best proven, best available.
RC: Best existing?
EC12: Best existing there's all different ways to skin a cat I guess.
RC: And are all valid?
EC12: That's not the issue in 29 so who cares if they're valid or not.
RC: Well, it is if you are using an active control and someone is saying "aha but you're not comparing this with the best current practice?"
EC12: Um…
RC: Or they might be saying "why are you using the best current practice?"
EC12: No I agree I agree.
RC: … when you're doing a study in [developing country] … you know.
EC12: I agree I agree. Again I agree. People are talking about it. But it's not why they are talking about it, it's not the issue. The issue is the problem of methodology of medical research. That's what's behind 29. That's what the issue is. "Best current", "best available", "best proven" doesn't change anything because the word "method" is so confused there that it's fantastic. It doesn't have to change.
RC: Okay.
EC12: I don't care what you right there, really, I don't care. It won't change anything. I mean… Again, I said it [at previous presentation], the importance of this document, the impact of this document is on the discussion. It's on the discussion. That's far more important than the practice…
RC: Right.
EC12: I know that this might not be the correct thing to say and it could be understood in the wrong way but certainly the discussion is more important and the decisions and specific practices, they cannot be determined simply from a document like this. No specific decisions… no specific decision in a research could be determine only by reference to Helsinki.
RC: Why would that be because some could certainly try?
EC12: Because … because an activity is a situated activity and there are many more things that impact on that activity than simply one document. It could not be that way. And if it was that way, it would entirely incorrect, it would be unethical. Because if it was only the Declaration of Helsinki involved then where's the patient and it's about the patient huh? So we have to have at least two things in that. And as soon as you bring in the 2nd variable, you have an enormous variable. It could never be about just Helsinki.
RC: The 2nd variable being the patient.
EC12: Yes.
RC: Thank you. The other question I would like… the Note of Clarification has come in for some criticism. Yesterday, someone pointed out the use of the Boolean operator "or" was incorrect because it seemed to open the door to compelling scientific reasons being justification for placebo-controlled studies which may lead to …
EC12: What other kind of reasons could there be?
RC: Ah, their argument was that it should be "and". (10min50sec) Not only should it be scientifically compelling but potential harm to patients by participating in placebo must also be minor or reversible.
EC12: It depends upon what you're studying.
RC: Right.
EC12: It depends upon what you're studying. If you're studying somebody who's a child with cancer at an advanced stage then this idea of a minor condition may not be relevant. It may not be relevant if the survival and all that changes. But anyway I don't, I'm not very interested about that debate. That's not for me. I mean I can play the game and walk the walk, that's okay… talk the talk but that's not … that's not what's going on in this thing and that would be wrong.
RC: One other comment that I've heard and would be interested in your comment on this is that it is wrong to call this a note of clarification because it doesn't clarify paragraph 29, it changes paragraph 29. It's an amendment, would you have a sort of response to that…

EC12: Well I wouldn't say it's ... it changes, it certainly changes the way we read 29 and it's an amendment in a sense of an addition. But the sentences remain the same. And the ... certainly 29 and the Note of Clarification say, as I read them anyway, 2 rather different things, but that's the intention.
RC: Right. Thank you. I think that's very helpful and your views on that are interesting. We'll now look at paragraph 30...
EC12: (laughs) Glad to be interesting.
RC: Well absolutely. And certainly what you've strongly emphasised I understand is the position that these are principles that guide the debate and as such they are general statements and the more specific protocols that guide the debate will be generated by that debate but shouldn't actually just stem from Helsinki on its own.
EC12: No, it's a cornerstone not an edifice.
RC: You don't go live in a cornerstone, you build a house on it a useful metaphor.
EC12: And also, the other thing is that it's more important to understand why the debate takes place. I mean that's my way of approaching it. It's not what people are saying always that's what's important, it's what underlies this concern.
RC: An example of a situation where you think that's ... it's not what they're saying but why they're saying it?
EC12: Well, 29 is a good example. It's because there is... what's really going on in 29 is ethics has come too close to critiquing scientific method. In fact there is no difference between placebo and another control arm. There's absolutely no difference neither from a scientific point-of-view or from an ethical point-of-view. If I give you a drug or if I give you something that looks like a drug, it doesn't matter if in the scientific equation, if in the RCT we have equipoise there's no difference at all, no absolutely no difference. So placebo's a no... it's an empty question. Problem is, by going in there, by Helsinki touching on that it has touched on a very fundamental problem ... or problematic with regard to scientific methodology. It's scientific methodology that's at stake at the end of the day in this question. It's not treatment. It's not best current, proven, anything.
RC: Let me understand... let me make sure I'm understanding you right, that the issue of equipoise obliterates the ethical issue involved in whether you are going to use active treatment or whether you are going to use placebo.
EC12: No difference right.
RC: So we have a situation where we have a condition. But we have an established, effective treatment for it.
EC12: Right.
RC: Say it's something destructive like rheumatoid arthritis. Say we have an established effective treatment that will prevent joint destruction. Someone comes along and says "I think I have a better one and I was to test it".
EC12: Right
RC: "But I'd like to test it against a placebo".
EC12: Right.
RC: Would that be ethically okay?
EC12: Well, would you have achieved equipoise in your trial? Well, that's the thing - you wouldn't have equipoise in that case.
RC: Thank you - that clarifies it.
EC12: It's not about placebo. It shouldn't be about that either. It shouldn't be about that.
RC: Thank you. I hear what you're saying. It's a point that's not taken up by many...
EC12: No, that's because people don't underst... they really don't understand, they genuinely don't understand what's at stake, because they ... basically what we do in medical research ethics is we justify... we try to provide justifications for something that is not justifiable and that is experimenting on humans. That is not justifiable. You could not justify that. And this is a very frustrating situation to be in. So this is what we're doing. This is...
RC: ... well we'll come back to that because there's a part of the text... we'll come back to that. (16min56sec) Paragraph 30 now I invite you to comment on up for possible amendment or

clarification but we have the text as it is which has caused a furore. Again the impact of this on conduct of research or debate or …
EC12: Again this is a problem of methodologies way behind this one but much more further. The only difference between 29 and 30 is 30 is even … 30 is a nonsensical sentence - it doesn't make sense. You could not … you could not apply it. And it's very unethical. You put the study in front of the patient. You put the product in front of the patient. You make the … it's about economics, it's about social justice or something but it's not about ethics. And you know at the end of a study many patients are dead. And you know at the end of a study many patients have been out of that study for 2 or 3 years. At the end of a study who says the study is relevant to the patient's condition. What are we talking about here? Are we just talking about AZT trials and certain ideals about them? But it's very… also paragraph 30 is written to benefit the pharmaceutical industry. It's written to benefit powerful research organisations. And it's very much against developing countries and …
RC: How so?
EC12: Because who could possibly provide access besides a resource-intensive institution at the end of a study? Why is the WMA telling researchers in poor countries that they cannot do research. I don't understand this.
RC: How then, you phrase it as it's written for the benefit of … you mean it's written with them as the target or written for their benefit?
EC12: Yeah, but every time in the Declaration of Helsinki or in CIOMS or wherever, every time somebody does something for the benefit of developing countries it always has the reverse effect. Every one of the … you can look at you will find that. If you think about what's actually going on there this is a disaster for these countries. The double standard is bad news. It's usually bad news for the people you are trying to benefit.
RC: Just trying to look further at your statement that this is written for the benefit of pharmaceutical companies.
EC12: Well it was not written, the authors did not have that in mind. They thought they were writing for the benefit of developing countries but it is written … what is achieves is to benefit industry to benefit powerful research organisations that have huge resources.
RC: How would they say this would benefit… most of them are worried about the ongoing commitment…
EC12: They're not worried about that.
RC: I've heard that asserted …
EC12: Yeah, I'm sure they will assert that too why not? Play the game. One of the things research is a market activity one of the things to do in a market is to control that market. Small biotech companies can't play in that market not as paragraph 30 is written.
RC: That's interesting. So really this is written for the benefit of the very large companies…
EC12: Yeah, big pharma…
RC: … who could perhaps come up with the goods for this and no-one could really compete.
EC12: That's right. That's the only… for example right now in [developing country] there is… the people are trying to put together a study to measure one set of AZ… antiretroviral regimens against another antiretroviral regimens. Paragraph 30 says you can't do that. I don't understand this. Why can't [this country] find a better way to treat their people? I don't understand it… it's beyond me.
RC: Okay and your thoughts on the proposed note of clarification the first sentence "this reflects the principle that those who take part in research should benefit from the…"
EC12: All the proposed notes, almost the whole of them - they're all nonsense, really they are because they are all about products. But my opinion … it's a secondary opinion of mine - so my sentence is "at the beginning and the conclusion of their participation in research, patients should be informed as to how they can receive the care most appropriate to their conditions". So it's at the beginning and conclusion of their participation, not the study - who cares about the study, that's not important to the patient "of their participation as to how they can receive the care that's most appropriate to their situation". That's what we need to do.
RC: And that would be a note of clarification or an amendment…

EC12: Let's just take out the old sentence and forget it ever happened.
RC: Thank you very much…
EC12: Okay… sorry to be myself…
RC: No problem - by all means, that's why we're here.
EC12: No problem in 19.
RC: 19?
EC12: Perfect the way it is.
RC: Has it had any impact …
EC12: Yes it has, I can give you direct impact that 19 has had.
RC: Tell me.
EC12: In that… in that text it says that you cannot do research on vulnerable populations if they cannot … if they will not give consent. Huge problem. You'd say everywhere else "How can we do research in emergency situations?" Right. They wanted to write the same thing in [specific piece of legislation] but there were two amendments proposed. And the … they wanted to write you … not to research on children unless it's in the interest of the child which would have meant a restriction on research in childhood – [example of exchange of advice naming specific individuals] – "quote paragraph 19 of the Declaration of Helsinki - use Helsinki as his argument". And the thing is now we do have that you can do research in children if it's in the interest of their population and I think everybody was …
RC: Thank you that's a very clear example. Thank you.
EC12: It's the only one I know where Helsinki has had a real direct impact on a specific decision like that but that is exactly what happened.
RC: Thank you. Well we're past the ones that have generated a major amount of controversy but many paragraphs have changed in significant ways and I'd be interested in your comment on a few more, right? One of the them's paragraph 27. This is an enhanced responsibility placed on both authors and publishers and it's… I'm particularly interested in an additional sentence relating to the publication of negative results. Now your thoughts on the …
EC12: Couple of thoughts. Helsinki often makes some mistakes. One of the mistakes in the 2000 version was to …
RC: That's the old version there yes…
EC12: It used to be… It used to say… Declaration of Helsinki … ethical principles… what was before that? … guiding physicians. Now says "for medical research involving human subjects?" And everybody came and said "Helsinki belongs to the world. It's important to the world". And the WMA heard that and they took it on and they shouldn't have done it. And so … so they wrote this sentence. They changed that and they should never have done that. They should always say this is for physicians by physicians. Who is the WMA to tell publishers what to do? They have no business telling publishers what to do?
RC: Presumably it's publishers who are also physicians?
EC12: But, no, still, they don't have any business because in his capacity as a physician they can tell him what to do. In his capacity as a publisher they can't tell him what to do.
RC: Even a medical publisher?
EC12: Yes. Because not all medical publishers are physicians. They should speak to the person in a deontological manner. This is what physicians should do. If the physician's a publisher, okay he still has an obligation but qua publisher not qua physician. So I do agree with 27. I think it would be great if we published negative data. I don't know who would be interested to publish negative data and I don't know who would always interested to read negative data…
RC: Meta-analysts presumably and people …
EC12: Yeah that's true.
RC: And people evaluating health …
EC12: Yeah, a few people would but we have to find… the problem is we don't have a structure for doing this. So the obligation is really what are you going to do you can put it on the internet that's publishing it. You can tack it on a tree, that's publishing in, but that doesn't mean you're going to

have the impact that you want. We don't have the structures in place for dealing with... actually we have a huge problem with data exchange and sharing information in medical science. (28min40sec) Researchers are no better than pharmaceutical companies at sharing information with one another, they're probably a lot worse, so we have huge problems. So I agree with the intent there. I agree with the idea that research is... doesn't take place in isolation. It does take place in society. Society has a right to be informed of the results of this type of activity. The question is how to do it and we don't have any structures in place to handle.

RC: Is it a reasonable thing to put in a 'cornerstone' a foundational or aspirational document?

EC12: I think that the 1st concern – it should say that they will be informed as how to the results of the research will be made available to them. It's a major concern. It's a huge concern especially in developing countries about how research results are made available to the participants and to their communities. It's a big big problem. I'm really concerned about this issue. And I would have started in the area of making the research results available to the participants and their communities.

RC: You mentioned something about - you liked the intent or you agreed with the intent. What do you see as the intent?

EC12: That science is not a private activity it's a public activity.

RC: And the benefits that would arise from that are publication bias would be...

EC12: I'm not too interested in this benefits stuff, sorry I don't want to go down that road because it's not ethics. That somebody else's discourse, I don't want it. Okay.

RC: That brings us then right back to the start of the document and I think you've already alluded to some aspects of this. Paragraph 1 has changed significantly because there is a sentence now which for the first time makes clear that the purvey, the remit of the Declaration of Helsinki applies to identifiable human data and identifiable tissue.

EC12: I have no problem with that. The problem is with a document like this, the more you specify the narrower you make your remit. Now it said before it was for biomedical research. Now you're going to give a definition of biomedical research. And everything you do not put in that definition falls outside of it. And this is a big problem. So paragraph 2 should be paragraph 1 because that is what's at stake. That is a brilliant... that is poetry... I mean 2nd sentence of that paragraph, that's about as close to Shakespeare as you are going to get.

RC: 'The physician's knowledge and conscience are dedicated to this end'.

EC12: This is such incredible thinking and not only for that reason but for the order of thinking, the order of structuring the text and so forth, that should have been the 1st sentence. Who cares? But I mean that's what it should have been. (32min06sec) You don't need paragraph 1. It's absolutely useless. You only need 19(?).

RC: Now I've heard it said that one of the reasons for paragraph 1, and I take on board your point about not specifying too much because everything then falls out that's not specified, was that it sets out the reasons for the Declaration of Helsinki which then got taken up in paragraph 2 so maybe it should be a pre-amble I don't know, is that it's a statement of ethical principles to give guidance. And I've heard that described as in fact it's not a set of statutes, it's not a detailed set of procedures.

EC12: That's what said in the sub-title why do you want to repeat it? What does that give you? It just lessens it. It just weakens it. That's not good writing.

RC: That's fine no I just wanted your opinion on it...

EC12: Do you have 9? What else?

RC: 9 and 6 are the other specific ones I'm going to.

EC12: You don't have 13?

RC: I'm not going to 13 specifically but I give you the opportunity...

EC12: Well, I'd take it anyway (laughs). 13 was, was, it still is in a way, it was a brilliant, brilliant paragraph and then they got this issue about conflict of interest that they got uptight about and it happened everywhere. And they just weakened the heck out of the paragraph. Do you realise now an ethics committee according to the Declaration of Helsinki is obliged to review adverse events, serious adverse events but it's not obliged to review informed consent. See when you specify but you don't think about what you're doing, you end up with this situation.

RC: So it's gone too prescriptive, too specific.
EC12: They got overly excited about conflict of interest. They don't have to write... they could have written a small sentence about conflict of interest instead of putting it in different places and not thinking about what they were writing.
RC: So I don't hear from you or from any people that there's any issue that conflict of interest is an issue that should be addressed but that what you're saying is that it's overly specific and overly repetitive because it's also mentioned in paragraph 27 as well.
EC12: 27 is it mentioned?
RC: 27 mentions it in publication, the publication...
EC12: Oh yeah, and it also mentions it in informed consent. Which is another disaster. They list... you know you have to disclose conflict of interest right but you don't have to tell the patients here ... I don't know there are so many things that are missing.
RC: So that by the fact that they've put some things in and not put others in...
EC12: So for example you don't have to tell the patient what other treatment might be available to them, it's not in here. Is that more important ... is that less important than conflict of interest? Is conflict of interest such a big deal really?
RC: Yes, I'd like to hear your views on that. (35min39sec)
EC12: I mean ... anyway these sort of things... but anyway the text could be better written. Let's go to 9.
RC: I'd like to draw your attention to a big change. Previously it must be standards as drafted are only a guide to physicians all over the world, and they are not relieved from criminal, civil and ethical responsibilities under the laws of their own country. That has now changed to no national ethical, legal or regulatory requirements should be allowed to reduce or eliminate the protections for human subjects in this document.
EC12: Right. That's a better sentence. That's a good improvement to Helsinki. What are people saying? Some people are really up in arms about this. How dare they? How dare they say that Helsinki is more important than national law? Can you imagine? How dare they say that? But I think... I don't know... I don't know the discussion behind this but my sense is that the discussion behind this is to protect physicians when they get in difficult situations to say 'no I can't do this. I can't be part of this. And they have to be protected'. And this is fantastic.
RC: Can you think of examples where...
EC12: Why should ... why should law be above ethics, or why should ethics be above law... I mean why is law always above... I don't understand and I have no idea about that.
RC: Now one colleague of ours raised an issue about the fact that... now many have pointed out that this does help for physicians in countries especially like where there's rapid change and a vacuum of legislation and protection ...
EC12: Yeah, I understand what's being said there... (pause) I still think this is more important because the law could... I don't think, I can't think of a law that would say 'you should torture people' but I can think of a law that might say 'well, you know in the case of non-combatant fighters you can do whatever you want to do with them because these are not really human beings anyway'. I can think of situations like that rather clearly.
RC: Well thank you I think this is a clear statement that you feel that this has improved things.
EC12: I think it's much... I don't want to go down the road of improvement but...
RC: Sorry it's an improved statement... not improvement necessarily...
EC12: Yeah I think it is good for the text, and it's good for Helsinki. I can live with it yeah, quite easily.
RC: Now paragraph 6 ...
EC12: I'm glad you mentioned paragraph 6 because nobody ever talks about paragraph 6, why don't they do that.
RC: Well that's an interesting...
EC12: Has anybody ever... have you ever seen anybody write about paragraph 6? Has anybody ever mentioned paragraph 6 to you before you did?

RC: No.
EC12: And it's the most radical change in all of Helsinki. It's absolutely enormous because... and this sentence - I don't know where you could ever find this sentence anywhere else that you must do research. It's an ethical requirement to do research. Do you know of another text that says that?
RC: I know of other texts that say that research is justified by the benefits ...
EC12: No no that's something different.
RC: That's different.
EC12: That's the justification for research but a text that says 'as a physician you must do research', I've never seen that and I agree entirely with it except the word 'continuously', it should be 'continually'. That's the only difference.
RC: Yes, that's an interesting...
EC12: You can't do that 24 hours a day, 7 days a week, you might get tired.
RC: ... but continually yes would help with that. Another issue that arises in that sentence is the choice of the 4 criteria by which new methods should be challenged.
EC12: I think it's fantastic.
RC: Some have questioned the fact that safety isn't in that list.
EC12: Efficiency includes safety from my point-of-view but I would have guessed people would question that. But I think safety is part of efficiency but anyway if you wanted to clarify, you wanted to add safety I'd have no problem.
RC: Others have criticised the use of the word quality as being too vague.
EC12: I think with efficiency you have effectiveness as well so you could actually reduce it from my point-of-view.
RC: But quality has been in effect accused of being a bit too vague...
EC12: Quality is enormously important I know and people will learn that it's important. There are quality issues with regard to medicines and there are... no quality is a good thing for me.
RC: Well that's the last of the specific paragraphs (41min49sec) I draw your attention but I would like to get your comment on the revised structure of the document the elimination of the therapeutic/non-therapeutic dichotomy and the restructuring into basic principles and then additional principles.
EC12: Sorry I didn't get the first part, what was the first part?
RC: All the previous versions of the Declaration of Helsinki divided research into therapeutic or non-therapeutic. This document eliminates that dichotomy and re-structures it into here are basic principles that apply to all medical research and here are additional principles when clinical care and research are combined.
EC12: Yeah, that's the part I didn't get. I don't get see any re-structuring of the document.
RC: I guess I see it as... let me draw. Previously what happened was... this is the realm of research and it's either non-therapeutic or it's therapeutic. And we've got rules for this and rules for this. You know this is healthy volunteers and aviation medicine studies and all that sort of thing where you're not treating patients, you're just looking at physiology or safety you know phase I studies. Now it's saying 'okay instead of having this list and this list, here are some basic principles that apply to all research and here are research plus clinical care. So the basic principles still apply but there's a few extras thrown in when you've got a scenario where it's your patients that you're researching.
EC12: I'm just saying basically I don't think they really changed it. It's a ... they played a game. I don't think they really changed because additional principles for medical research combined with care. These I agree they insist adding ... they still have therapeutic/non-therapeutic distinction, they just made it different.
RC: And where does that appear? Therapeutic/non-therapeutic.
EC12: Well because A and B applies to everyone and C only applies in therapeutic situations.
RC: Now some have argued that there are some situations in which you know non-therapeutic especially assessment beforehand of risks and benefits that apply more specifically in non-therapeutic situations and that what has happened is the protections of healthy volunteers for example, or

participants in other types of non-therapeutic research have been reduced, would you see that as having validity?
EC12: Oh I think that part of the ... we do focus on ... when we focus, these discussions do focus on people with a condition that's relevant to the research. Yeah, and we really do miss phase I studies and things like that. But I don't worry too much about it because things are okay the way they are right now.
RC: In terms of the conduct of phase I studies or are we okay in terms of the text.
EC12: No in terms of what the text ... the impact of the text on a phase I study, you know for example 30 makes no sense in terms of a phase I ... but then phase I is non-therapeutic so it doesn't apply because that's a therapeutic study so they've just changed the language. ... And I agree with that argument it's not really relevant. But they didn't realise when they ... tried to dump this on the World Medical Association, was many countries have based their laws and their thinking about this on the distinction between therapeutic and non-therapeutic so the attack was not only against Helsinki it was actually a fundamental attack against some national approaches to research. ... And I agree they did structure them a little bit differently, you can paint the picture that way, but there's still the distinction between therapeutic and non-therapeutic. They had to maintain that.
RC: Thank you. Well my last and I do have one general question after this...
EC12: Any other comments?
RC: Yes, things I've left out in the text that you'd like to make a comment on and general comments.
EC12: No I think I've done enough damage here. No I think... no I'll stick to no changes.
RC: Not at all.
EC12: No I think it's a ... I like ... Helsinki is a fantastic thing, it's fantastic. Even the mistakes are fantastic. You can you know like it says here the primary purpose is to improve therapeutic procedures and the understanding of... well the logical order would be 'the primary purpose of research is to improve understanding and procedures...' but if you really go back and think about it very often we improve our procedures before we improve our understanding so even ... every place where there is a confusion in Helsinki or a misunderstanding, what's really good about it is you can see that confusion, that misunderstanding or whatever reflected in the practice of research in the world. So more power to it.
RC: Well thank you very much. And finally just a general question and this is just really an important consideration given that I'm interviewing people from several different parts of the world and several different viewpoints and perspectives with respect to the ethics of medical research and it's a moment's self-reflection in which I just ask you to reflect on and comment on how it is you think you personally have come to hold the views that you hold about the Declaration of Helsinki and the ethics of medical research and which...
EC12: I think by talking by talking to people like you. I think it's education. I think it has to do with experience in general. Whatever my experiences have been with the world, that's formed my views I suppose. Some kind of dialectic. Some kind of dialogue I suppose.
RC: Well thank you.
EC12: Thank you very much.
(END OF INTERVIEW)

APPENDIX 9: PUBLICATIONS ARISING FROM THIS THESIS

The following are the publications that have, so far, arisen from this thesis.

(1) Carlson RV, Boyd KM, Webb DJ. The revision of the Declaration of Helsinki: past, present and future. *Br J Clin Pharmacol* 2004; 57: 695-713.

This arises primarily from the material in Chapter 2.

(2) Carlson RV, van Ginneken NH, Pettigrew LM, Davies A, Boyd KM, Webb DJ. The Three Official Language Versions of the Declaration of Helsinki: What's Lost in Translation? *J Med Ethics* 2007; 33: 545-548.

This arises primarily from the material in Chapter 5.

(3) Carlson R, Boyd K, Webb D. The Interpretation of Codes of Medical Ethics: Some Lessons from the Fifth Revision of the Declaration of Helsinki. In: Schmidt U & Frewer A (eds.). *History and Theory of Human Experimentation: The Declaration of Helsinki and Modern Medical Ethics.* Stuttgart: Franz Steiner Verlag, 2007. pp.187-202

This arises primarily from the material in Chapter 4.

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The revision of the Declaration of Helsinki: past, present and future

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The World Medical Association's Declaration of Helsinki was first adopted in 1964. In its 40-year lifetime the Declaration has been revised five times and has risen to a position of prominence as a guiding statement of ethical principles for doctors involved in medical research. The most recent revision, however, has resulted in considerable controversy, particularly in the area of the ethical requirements surrounding placebo-controlled trials and the question of responsibilities to research participants at the end of a study. This review considers the past versions of the Declaration of Helsinki and asks the question: How exactly has the text of the Declaration changed throughout its lifetime? Regarding the present form of the Declaration of Helsinki we ask: What are the major changes in the most recent revision and what are the controversies surrounding them? Finally, building on the detailed review of the past and present versions of the Declaration of Helsinki, we give consideration to some of the possible future trajectories for the Declaration in the light of its history and standing in the world of the ethics of medical research.

troduction

ıe Declaration of Helsinki (DoH) is, indisputably, a markable document. In less than 2000 words, the orld Medical Association (WMA) spells out a set of hical guidelines for physicians and other participants medical research. At the recent Scientific Session held association with the WMA's annual assembly, various lependent experts on research ethics confirmed the ntral role of this document. At this meeting the DoH ıs described as the 'cornerstone' document pertaining to medical research ethics [1] and as 'the most widely recognized source of ethical guidance for biomedical research' [2]. Yet the DoH's guideline statements are not without controversy; and even more so since the most recent revision at the 16th Annual Assembly of the WMA in Edinburgh in October 2000.

In this paper we review the past and outline the present form of the text of the DoH. The major changes in the Edinburgh (2000) revision are outlined, along with some of the controversies to which they have given

rise. Finally, we consider the possible future trajectories for this important document. Throughout this article we focus on the text that emerges at each stage of the process. The process leading to each revision is now extensively documented by the WMA at its own website [3]. We aim, through this review, to familiarize the reader with the current content of the DoH and an historical understanding of how the Declaration has changed with each revision. In so doing our hope is that awareness of the ethical issues for doctors participating in medical research will be heightened and that more will be encouraged to join the debate to ensure that this document remains an important guiding set of principles for many years to come.

We recognize that there is a major issue in modern philosophy regarding whether the meaning of a text is inherent in the author's intent or in the reader's interpretation [4]. Philosophers Hans-Georg Gadamer and Paul Ricoeur essentially take the position that the text has a mediating function seeking to fuse the horizons of understanding of author and reader [5]. Since, for the most part, researchers and others seeking to implement the guiding principles of the DoH have not attended WMA meetings and have no easy means of access to the 'intent' behind the text as it emerges, we consider it essential to take a stance akin to that of Gadamer and Ricoeur. Thus our emphasis is on the text which emerges rather than the debate which leads to the text. In this instance, however, the 'author', the WMA, is able to monitor both changing events in medical research and readers' response to and interpretation of the DoH and the Declaration can be modified accordingly. This was explicitly stated in the 1975 version of the DoH: '[the recommendations] should be kept under review in the future' (see Appendix 2). Although the Edinburgh (2000) amendment saw this statement removed, in this sense, at least, the DoH can be conceived of as a 'living document'.

Declaration of Helsinki: past

The *British Medical Journal* announced the emergence of the DoH in its 18 July 1964 edition with the following words: 'A draft code of ethics on human experimentation was published in the British Medical Journal of 27 October 1962. . . . A revised version was accepted as the final draft at the meeting of the World Medical Association in Helsinki in June 1964. . . . *It is to be known as the Declaration of Helsinki*' [6] (emphasis ours). Attached to this inconspicuous announcement was the just over 700 words of the text of the original DoH. There seemed little indication at the time of how important this document would become in the context of research ethics.

One of the darkest episodes in the history of medical research – the horrific experiments carried out by doctors on concentration camp victims in Nazi Germany – was exposed at the Nuremberg trials of 1947. Emerging from the Nuremberg trials was a code of ethics setting out 'standards to which physicians must conform when carrying out experiments on human subjects'. The original DoH is seen as having its roots in the Nuremberg Code (see Appendix 1). Fluss identifies 12 markers of ethical research within the Nuremberg Code [7]. He points out that, of these, 10 markers appear in the original DoH and two markers are abandoned. The Nuremberg requirement that 'The voluntary consent of the human subject is absolutely essential' is changed and the DoH allowed consent to be given by the 'legal guardian' in cases of 'legal incapacity'. The other abandoned 'marker' was the statement 'During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible'. This somewhat confusing statement was eliminated in the original DoH and appears to be covered most closely by the sentence: 'The investigator or the investigating team should discontinue the research if in his or their judgement it may, if continued, be harmful to the individual'. This is, of course, in addition to the subject or subject's legal guardian's freedom to withdraw consent at any time [8].

The original DoH also states 'In the field of clinical research a fundamental distinction must be recognized between clinical research in which the aim is essentially therapeutic for a patient, and clinical research the essential object of which is purely scientific and without therapeutic value to the person subjected to the research' [8]. This led to the fundamental structure of the document. The paragraphs of the original and the first four revisions of the DoH are grouped under the headings 'Introductory statements', 'I. Basic principles', 'II. Clinical research combined with professional care' and 'III. Non-therapeutic clinical research'. This structure persisted until the Edinburgh (2000) revision when it was substantially revised, and we return to this issue under 'Declaration of Helsinki: present'.

First revision: Tokyo (1975)

The first revision to the DoH was adopted by the WMA at its 29th annual assembly in Tokyo (1975). This document was drafted by three Scandinavian professors of medicine [9].

The document was extensively revised from the 1964

version. Arguably the single most important addition in terms of the ensuing conduct of medical research was the requirement that independent committees review research protocols. Another major development was a significant elaboration of the requirements for informed consent. These requirements were also moved to the section entitled 'Basic Principles' (see Appendix 2; paragraphs I.9–I.11). Additional considerations regarding informed consent are presented in the section pertaining to 'Medical Research Combined with Clinical Care'. These changes coincided with a simplification of the consent requirements for 'non-therapeutic' research wherein it is now simply stated 'The subjects should be volunteers' (paragraph III.2). Since the elaborated principles in the section 'Basic Principles' apply both to the 'Clinical' and to the 'non-therapeutic' category of research, there was no net loss of protection for subjects.

Table 1 outlines summary statements of the most important changes which took place in the 1975 revision. Appendix 2 gives the full text of the 1975 DoH. In addition to the major changes in content, there was a revision of the overtly sexist language in the 1964 version. The phrase 'fully qualified medical man' was changed to 'medically qualified person' (see paragraph 3) and the use of the pronoun 'his' in reference to 'doctor' in the 1964 version was changed to 'his or her'.

The revision which took place in 1975 was even more extensive, as a proportion of the starting document, than the Edinburgh (2000) revision. Almost nothing was removed from the 1964 version and much was added. The result was an almost doubling in the length of the document. Given the relatively minor revisions of 1983, 1989 and 1996 (see below), it is effectively the 1975 version of the DoH which became the guiding document for the ethics of research involving human subjects for a quarter of a century.

Table 1
Key changes in the Tokyo (1975) revision of the Declaration of Helsinki

Introduction	
3rd, 4th and 5th paragraphs	Nature and purpose of medical research
6th paragraph	Respect for environment and for animals used in research
7th paragraph	Keep Declaration under review
Basic Principles	
I.2	Independent committee review of research protocols
I.5	Interests of human subject must prevail over interests of science and society
I.8	Obligations regarding accuracy in publishing
I.9–I.11	Enhanced requirements for informed consent
I.12	Protocol must declare that requirements of Declaration of Helsinki adhered to
Medical Research Combined With Professional Care (Clinical Research)	
II.2	Best current therapy should be comparator arm
II.3	Assurance of access to best proven methods
II.4	Refusal of research participation not to affect doctor–patient relationship
II.5	When doctor considers it is essential not to obtain informed consent*
Non-therapeutic Biomedical Research Involving Human Subjects (Non-clinical Biomedical Research)	
III.2	Less detail regarding consent (most of detail moved to Basic Principles section)
III.4	Well-being of subject takes precedence over interests of science and society (see I.5)

**This is the only paragraph from the 1975 (and subsequent minor revisions) completely removed at the Edinburgh (2000) revision. (N.B. These are listed under the numbering system of the paragraphs in the Declaration with the exception of the 'Introduction' section, which is not numbered.)*

Second revision: Venice (1983)

Given the extensive nature of the revision in 1975, it could be argued that the very minor changes of 1983 hardly warrant the term revision. However, it is the practice of the WMA in respect of the DoH to list all amendments in the preamble to the Declaration with no indication whether the amendment was major or minor. This practice has only been varied with the addition of the Note of Clarification to paragraph 29 in 2002 which is mentioned in the preamble (see Appendix 3) but not described as a revision, since the text of the actual paragraphs of the Declaration did not change.

In 1983 there were four fairly minor changes to the text of the DoH [10]: the word 'doctor(s)' was changed to 'physician(s)' in the 16 instances where the word occurred in the 1975 version. In the 'Introduction', the quotation from the Introduction from the International Code of Medical Ethics changed slightly as the wording of this code had changed. Also in the 'Introduction', the Latin phrase *a forteriori* was changed to 'especially' in the statement 'In current medical practice most diagnos-

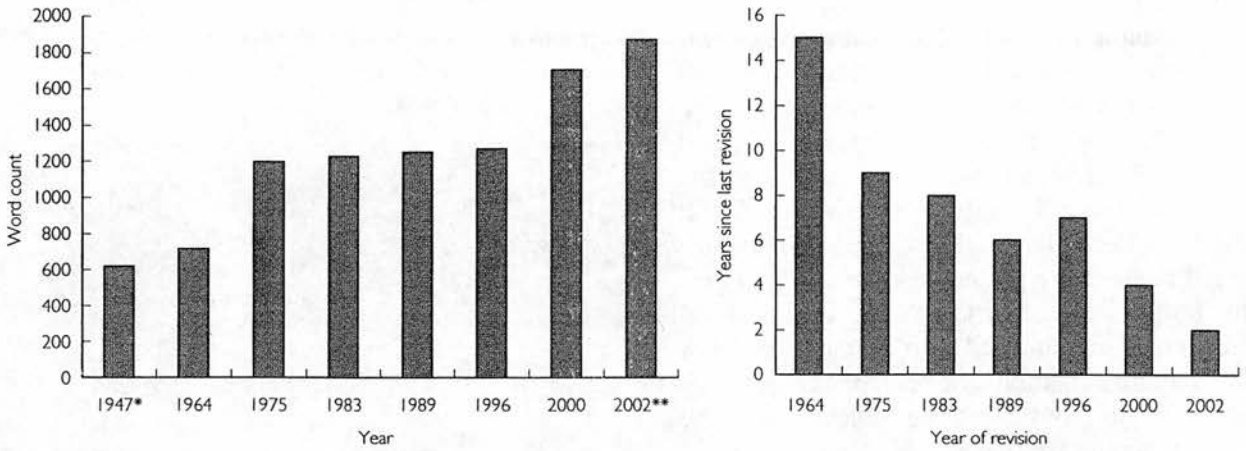

Figure 1
Word count for each revision of Declaration of Helsinki and years since last revision. *Nuremberg Code, **Includes Note of Clarification

tic, therapeutic or prophylactic procedures involve hazards. This applies *especially* to biomedical research'. Finally, in the 'Basic Principles' section, the requirement that where a minor is able to give 'a consent' that such consent should be sought was added to paragraph I.11 dealing with situations of legal incapacity for consent.

Since nothing was removed from the document, these minor revisions led to an increase in the length of the document, which now comprised just over 1200 words (see Figure 1).

Third revision: Hong Kong (1989)

This revision requires a fairly careful reading to see where any difference at all occurs. The only change in wording which occurs is in paragraph I.2 under the section 'Basic Principles'. Previously the Declaration required that experimental protocols 'should be transmitted to a specially appointed independent committee for consideration, comment and guidance'. This was considerably elaborated in 1989. Protocols were now to be 'transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed' [11].

Given the requirement, as already stipulated in the introduction, that 'physicians are not relieved [by the DoH] from criminal, civil and ethical responsibilities under the laws of their own countries', it has to be questioned whether the additional requirements in paragraph I.2 are unnecessarily repetitive. It should be acknowledged that such repetition is not without precedent. From the Tokyo (1975) revision reference to national legislation is made in the paragraphs referring to informed consent. It could be argued that the use of repetition stresses the need for reference to national legislation in the instances in which it occurs.

Overall, the effect of the minor revision in 1989 added 29 words to the length of the DoH (Figure 1).

Fourth revision: Somerset West, South Africa (1996)

As in 1983 and 1989, the actual changes to the text were minimal. However, the nature of the small textual change provided a seed out of which grew a much larger debate. In 1996, at the 48th General Assembly [11, 12], the WMA adopted the following addition (shown in italics) to paragraph II.3 in the section pertaining to 'Medical Research Combined with Clinical Care (Clinical Research)':

'II.3 In any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method. *This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists*'. [Italics ours]

This occurred in the context of rising disquiet about the use of placebo controls in studies of materno–fetal HIV transmission. It is the first time the DoH makes reference to any specific type of research methodology, i.e. the placebo-controlled trial. A careful reading of paragraph II.3 without the addition would appear to have the same requirement on researchers, but for the first time the DoH refers specifically to placebo. It is the addition of this specific requirement that meant that the Food and Drug Administration of the USA chose to

continue to refer to the 1989 version of the DoH in its regulations [13]. This brings us neatly to the present version of the DoH with its attendant controversies.

The Declaration of Helsinki: present

We do not outline every detail of the textual changes, ince only three of the 32 paragraphs are completely inchanged, while eight are completely new [14]. Also, ince our focus is on the text of the Declaration, the vents surrounding the eventual Edinburgh (2000) mendment are not reviewed here. They are described n detail by Human and Fluss in documents readily ccessed at the WMA website and the interested reader ; directed there [15, 16].

We single out for comment the revised structure of the ocument, the most controversial of the new paragraphs 19, 29 and 30 – and four other paragraphs (1, 6, 9, 27) /hich, although they have not yet given rise to signifiant debate in the literature, are striking changes in the 'ay the document addresses aspects of medical research thics. The text of the DoH, Edinburgh (2000) revision ; appended to this paper (Appendix 3). Since we have escribed above all of the (very minor) changes that ook place in 1983, 1989 and 1996, the interested reader an, by referring to these and the two full versions ppended, see all of the changes in the Edinburgh (2000) evision.

restructured document

n all versions up to the 2000 revision the following tructure applied to the document: there was an Introduction (where the paragraphs were not numbered) followed by numbered paragraphs under the headings of Basic Principles', 'Medical Research Combined with Professional Care (Clinical Research)' and 'Non-herapeutic Biomedical Research Involving Human Subjects (Non-clinical Biomedical Research)' (see Appendix 2; the 1975 version of DoH illustrates this tructure).

The 2000 version of the DoH is completely restructured. There is now a section headed 'Introduction' comprising paragraphs 1–9 which sets out the scope of he document and some of the underlying principles. Although many of the statements in the 'Introduction' /ere present in previous versions of the Declaration, ıey have been re-ordered to present a more logical equence of reasoning. Arguably one of the most important statements is the requirement in paragraph 5 that In medical research on human subjects, considerations elated to the well-being of the human subject should ake preference over the interests of science and society'. By the end of the 'Introduction' the document has very clearly set up the dilemma that gives rise to the need for clear thinking about research ethics. On the one hand, it would be unethical not to challenge current methods in medical practice (paragraph 6) through research. On the other hand, it is wrong to simply use people as a means to an end (paragraph 5), particularly vulnerable people (paragraph 8). Having described this ethical tension in the 'Introduction', the DoH then seeks in the next two sections to articulate the guiding principles for deciding what research meets the ethical standards required and what does not.

After the 'Introduction', there follow paragraphs 10–27 under the all-encompassing heading 'Basic Principles for All Medical Research'. Finally, there are an additional five paragraphs (28–32) under the heading 'Additional Principles for Medical Research Combined with Medical Care'. It is in this section that we find the controversial paragraphs 29 and 30.

This is a major logical re-framing of how the DoH categorizes different types of research involving human subjects. The pre-2000 versions of the Declaration effectively dichotomized research into therapeutic (potentially benefiting the subject directly) and nontherapeutic (no direct benefit to subject). In the Edinburgh (2000) revision the new category of 'Medical Research Combined with Medical Care' is recognized as a subset of 'all medical research involving human subjects'.

There is no longer any specific section dealing with 'Non-therapeutic' research, which is often viewed as synonymous with 'healthy volunteer' research. There is specific reference to 'healthy volunteers' in three paragraphs of the Edinburgh (2000) revision. Paragraph 16 explicitly states that participation of healthy volunteers as research subjects is permissible. Were this not stated, then a certain way of interpreting paragraph 19 may lead to the conclusion that such research was now proscribed. In paragraph 18 healthy volunteers are identified as a group where the importance of prior weighing of the importance of research against its risks and burdens is especially important. Finally, Paragraph 8 in the 'Introduction' lists 'those who will not benefit personally from the research' among those groups that are vulnerable and in need of special protection.

This revision of how research is categorized has been strongly supported by Levine [17] as removing a previously illogical distinction. It must be of concern, however, that there is no longer a section of the DoH dealing with research where there is no potential benefit to the participants. Such groups do present some differences in methods of recruitment and such participants are often paid for their participation in research. These issues need further consideration and debate.

Paragraph 29: The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists (See Appendix 3 for Note of Clarification) As already mentioned, the 1996 version of the DoH is the first version of the DoH to mention specifically the use of placebo in trials. Paragraph II.2 from the 1996 version stated 'The potential benefits, hazards and discomfort of a new method should be weighed against the best current diagnostic and therapeutic methods'. This has been changed to the wording seen in the first sentence of paragraph 29 (above). The sentence which then followed in the 1996 version (and which formed the first sentence of paragraph II.3) stated 'In any medical study, every patient – including those of a control group, if any – must be assured of the best proven diagnostic and therapeutic method' has been eliminated. Finally, in the 2000 revision very little is changed in the actual sentence referring to placebo which is the second sentence in paragraph 29 (above); the words 'inert placebo' from the 1996 version are changed to 'placebo, or no treatment'. In a careful reading of the two versions, however, it appears that very little has changed in the overall ethical guidance with respect to placebo use. Therefore, what is surprising is that the outcry following the 2000 revision far exceeded the response to the 1996 revision.

The overall effect of paragraph 29 would seem to rule out use of placebo wherever proven treatment exists. As mentioned, this raised such a cry of protest that the WMA took the unprecedented step of issuing, in 2001, a Note of Clarification to Paragraph 29. The Note of Clarification was formally adopted as part of the DoH in 2002, although the WMA has not described this as a 'revision' since the actual text has not been modified – only 'clarified'!

However, the Note of Clarification certainly seems to modify the requirements and represents the first occasion where the WMA have issued explanatory text indicating the intent behind a specific paragraph. One of the best summaries with respect to placebo use in trials is that of Emanuel and Miller [18], who define three broad positions: placebo orthodoxy, active-control orthodoxy and the 'middle ground' (see Table 2 for definitions). It would appear that the Note of Clarification moves the stance of the DoH from what appears to be active-control orthodoxy towards the 'middle ground'. The debate in the literature over the ethics of placebo controls has raged for at least the past decade between the proponents of 'active-control orthodoxy' such as Rothman, Michels and Weijer [19–21] and those supporting 'placebo orthodoxy' such as Levine [22] and Temple [23].

The Note of Clarification lists two situations where placebo is acceptable: where there is a scientifically compelling reason, or where the condition under study is minor and the subject at no increased risk of serious or irreversible harm. These two situations are linked by the word 'or' which has been questioned by Macklin [2]. She asserts that the connector should be 'and' (i.e. both conditions must be fulfilled). The risk otherwise is that scientifically compelling reasons could be used to justify an increased risk of serious harm through use of placebo and this is argued to be inappropriate. This would be in line with the introductory principle of paragraph 5 that 'considerations related to the well-being of the subject should take preference over the interests of science and society'. The counterarguments are both that valuable research may be prevented [24] and that placebo-controlled trials often require a much smaller sample size and follow-up time and therefore expose fewer people to any risks inherent in the research [18].

A further issue with respect to paragraph 29 has been

Table 2
Emanuel and Miller's three ethical positions with respect to placebo-controls [18]

Active-control orthodoxy	Placebo orthodoxy	Middle ground
'Whenever an effective intervention . . . exists, it must be used in the control group . . . placebo controls are inappropriate because the clinically relevant question is . . . whether [a new drug] is better than standard treatment'	'When effective treatments exist, there must be compelling methodological reasons to conduct a placebo-controlled trial'	'Without a placebo group to ensure validity, the finding that there is no difference between the investigational and standard treatments can be misleading or uninterpretable'

the interpretation of the words 'best current' as the standard of comparator arm. Does this mean best in existence or best available in a local context? The Note of Clarification does not address the issue. The UK Nuffield Council on Bioethics argues the issue extensively, recognizing that 'The Declaration of Helsinki (2000) is the primary source of guidance on which the majority of other guidance draws' [25]. Their conclusion regarding the interpretation of 'best proven' is that 'the minimum standard of care that should be offered [in the control arm] is the best intervention available as part of the national public health system'.

There is still considerable discussion around the circumstances in which placebo control is ethically acceptable. It seems clear that for some serious conditions where there is often 'one chance' at cure – such as many forms of cancer – placebo-controls should be ruled out. At the other end of the scale, except for the most extreme adherents to 'active-control orthodoxy', minor and self-limiting conditions seem to present little problem regarding placebo use. It must be remembered that paragraph 29 refers to 'proven' treatment, not 'active' treatment. Just because a pharmaceutical agent is shown to have pharmacological 'activity' does not mean it has been properly 'proven' to be superior to placebo. Indeed, such proof may never be forthcoming in some conditions where placebo response is either high or greatly variable. Symptoms of chronic stable angina, for example, can show a highly variable placebo response [26] and this condition is selected by Emanuel and Miller [18] as an example where a well-designed placebo-controlled trial should be satisfactory on ethical grounds provided patients are well monitored for worsening symptoms, that appropriate 'rescue' or 'escape' medication is available, and participants are fully aware of their right to withdraw from the trial at any time.

In the middle of these extremes are many clinical scenarios where the issue of whether placebo-controlled research is acceptable or whether serious or irreversible harm is risked needs to be undertaken on a 'disease-by-disease' basis. Among the conditions which have given rise to recent debate in this regard are hypertension [27], depression [28], schizophrenia [29] and postmenopausal osteoporosis [30]. Taking osteoporosis as one example, Grody and colleagues [31] have pointed out that there are groups of patients in whom placebo-controlled trials clearly do not violate paragraph 29. They specifically identify as suitable for placebo-controlled trials: 'competent, well-informed patients [who] refuse approved therapies for sound reasons', situations where 'there is reasonable basis for substantial disagreement or lack of consensus among professionals about whether approved treatments are better than placebos', or 'subjects are refractory to known effective agents'. It should be noted, however, that this approach may introduce biases.

A person consenting to participate in any blinded randomized controlled trial is effectively agreeing not to be given information that most individuals would want to receive; that is, to know what treatment they are receiving at any one time. This agreement not to know such information is not unique to trials using placebo-controls. Placebo-controls are not deemed unethical in and of themselves by paragraph 29. What is called into question is the potential harm to research participants who may not receive otherwise available proven treatments during the course of a placebo-controlled study.

The issue of placebo-control, probably more than any other, highlights the need for delicate considerations to balance ethical tensions which often exist between research which seeks to obtain answers as efficiently as possible (and there is nothing inherently wrong with that) and the well-being of participants in research. The DoH, particularly in paragraph 11 but also in other places throughout the document, affirms that unless research constitutes 'good science' it is unethical. However, as already mentioned, paragraph 5 places an ethical onus on the doctor never to sacrifice the interests of the individual in the interests of science and society. At the same time paragraph 6 (and others) place an ethical duty on doctors to undertake research. Taking any of the paragraphs to an extreme while ignoring the other paragraphs risks either endangering the well-being of participants or placing catastrophic barriers in the way of medical advance, which has the potential also to rebound to harm the individuals. The process of independent ethical review (paragraph 13) and adequate informed consent (paragraphs 22–26) must serve to protect the participants. Ethics committees are charged with deciding what kind of control group is ethically justified in individual protocols and ought to do so in full appreciation of the ethical tensions described above.

So, despite the adoption of the note of clarification, there is considerable work to be done in clarifying in what circumstances placebo-controlled studies are ethically acceptable. It would be useful to see evidence-based guidelines like those developed for mood disorders [32] undertaken for a wide variety of conditions. This would greatly assist those designing research protocols and ethics committees in their required assessment of the risks and benefits (paragraphs 16–19). Of course, such guidelines, to be useful, would need to be

frequently updated to take into account medical advances.

Even after carefully thought out debate it is likely that there will still be those who would wish to see the Declaration interpreted in a way that would place greater restriction on use of placebo [33]. As Macklin cautions, 'Two paragraphs (29 and 30) . . . remain controversial and would still be controversial if changed to meet criticisms' [2].

Paragraph 30: At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study In the most recent edition of their highly successful textbook, *The Principles of Biomedical Ethics*, Beauchamp and Childress make the following observation: 'Until the 1990s, the paradigm for ethical analysis focused on the *risks* and *burdens* of research (emphasis theirs) . . . and on the need to protect potential and actual research subjects from harm, abuse, and exploitation. . . . However, a paradigm shift recently occurred . . . As a result, justice as *fair access to research* (both participation in research and access to the results of research) became as important as protection from exploitation' [34]. The most recent revision to the DoH, in particular paragraph 30 but also reflected in paragraph 19 (see below), would seem to bear this out. Nicholson asserts regarding paragraph 30 that 'this is potentially the most far-reaching of all the changes to the Declaration'. Concerns about the implications of paragraph 30 have led to the WMA assembling a Workgroup to consider either an amendment to the paragraph or the addition of a note of clarification. The report of the Workgroup was presented to the Council meetings which preceded the most recent WMA General Assembly (10–14 September 2003 in Helsinki) and it was decided that no amendment or clarification would be undertaken but that the Workgroup's deliberations would be continued and consultations widened [35, 36]. Although this decision has drawn criticism [37], we argue that it represents a 'sensible and measured' approach to the situation [38].

The debate centres around the issue of what happens to patients in a trial once the trial is over. Capron has characterized this as an example of the larger question 'who owes what to whom and why?' [39] In contrast to paragraph 29, where the critical question has been characterized as 'are participants worse off in the trial than they were before the trial?', the question here is 'are participants worse off after the trial than they were during the trial?'. Those who see paragraph 30 as imposing too great a burden on researchers emphasize the benefits which accrue to patients during a trial where there was no access to treatment beforehand and assert that nothing is lost (compared with the pretrial situation) if, at the end of the trial, the *status quo* resumes and access is lost. In contrast, those supporting paragraph 30 as it is emphasize the additional trauma and distress caused to patients who, after treatment for a duration of the trial, learn what is possible for them, only to be deprived of access when the *status quo* resumes post trial. They argue that these patients are, indeed, worse off after the trial than they were before. There is no easy way towards consensus on this and the WMA press release regarding the DoH following the 2003 General Assembly noted 'sharp differences of opinion over how to protect human participants in medical research' [35].

Other major changes in the Edinburgh (2000) revision

Paragraphs 29 and 30 have given rise to the greatest controversy. It is arguable that they may have overshadowed debate about other paragraphs which have changed significantly. Space does not permit elaboration in detail of every change in the 2000 revision, so we focus on significant changes introduced through paragraphs 1, 6, 9, 19 and 27.

Paragraph 1: 'The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data' Paragraph 1 outlines first of all the *raison d'etre* of the DoH. Although this statement has not changed from the earlier versions, it has been moved to become the opening statement of the DoH. However, the second sentence for the first time explicitly declares that the provisions of the DoH apply to identifiable human tissue and identifiable data.

Overall this paragraph has evoked little comment, although Riis has raised two concerns [40]. First, he considers that anonymized research should also be covered by the Declaration because of the possible harms associated with 'group stigmatization'. Second, he notes that there is 'brief mention of "human material" and "data" without including statements applicable to epidemiological and large-scaled genetics research'. Certainly the explicit inclusion of identifiable material and data has taken place without any considerations of the possibility of different requirements for consent later in the document, and this requires further consideration.

Paragraph 6: 'The primary purpose of medical research involving human subjects is to improve diagnostic and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality' The first sentence is not new to the 2000 revision of the DoH but the second sentence of paragraph 6 is entirely new. This places a distinct ethical burden on physicians to challenge current methods through research. The choice of the four criteria by which existing methods are to be challenged (effectiveness, efficiency, accessibility and quality) is not further justified nor are the actual criteria defined. However, to many readers who would see documents such as the DoH as placing obstacles in the way of research, paragraphs such as this explicitly describe the very real ethical tension which exists and which is described as balancing the protection of, and respect for, research patients and healthy volunteers with the necessary freedom of research to facilitate scientific progress as a public good' [40].

Paragraph 9: 'Research investigators should be aware of the ethical, legal and regulatory requirements for research on subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration' To understand the sea-change which this statement represents we need to consider the paragraph which was included in all previous versions of the DoH: 'It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries'. From previously being seen as guidance which did not in any way supercede national regulations, the DoH has recast itself as a minimum set of international standards 'binding' physicians worldwide.

It is perhaps very surprising that this paragraph has not given rise to greater controversy. The issue of the relationship between law and ethics is complex. However, it is noteworthy that the WMA in 2003 issued their own statement on the matter: 'In some cases the law mandates unethical conduct. The fact that a physician has complied with the law does not necessarily mean that the physician has acted ethically. When the law is in conflict with medical ethics, physicians should work to change the law. In circumstances of such conflict, ethical responsibilities supersede legal obligations' [41]. This statement by the WMA applies broadly to the relationship between ethics and the law and is not limited to observation of the DoH. This statement of course gives no guidance to the physician in the situation where two ethical codes conflict. What should a physician of devout religious persuasion do, for example, if he or she believes that something in a secular ethical code is not in harmony with an ethical code mandated by their faith? However, it is noteworthy that the Declaration of Helsinki itself has remained relatively free of any objections to it on the grounds that it clashes with other codes of ethics.

Paragraph 19: 'Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research' This is another statement which projects the concerns of the DoH into the realm of social justice. There are those who argue that this is not an appropriate role for the DoH [13] and others who argue strongly that the DoH should play a major role in combating what have been described as 'double standards' in the world of medical research [2]. Issues surrounding this debate have been discussed under 'Paragraph 30' above. Although not giving rise to the same degree of controversy as paragraphs 29 and 30, there was sufficient debate about this paragraph to warrant calls for a Note of Clarification and documentation was prepared in this regard [42]. It was, however, decided by the WMA Council in May 2003 not to proceed with a Note of Clarification to paragraph 19.

Paragraph 27: 'Both authors and publishers have ethical obligations. In publication of the results of research the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication' Of the four sentences in this paragraph, the first and the last were present in previous versions and will not be discussed further. The third sentence, requiring disclosure of potential conflicts of interests, has parallels in paragraphs 13 and 22. The overall result is that such potential conflicts must be disclosed to: (i) the committee undertaking independent review, (ii) the patient when informed consent is sought, and (iii) any research publication. Although the question of what constitutes a

conflict of interest is not fully defined, there seems little objection to the inclusion of these requirements in the DoH.

The requirement to make negative results available also seems to raise little objection, but should be recognized for the important advance that it is. As pointed out by Godlee, 'Negative results are just as important to scientific understanding, if less exciting for researchers and editors, as positive studies'. She asks 'What has publication bias to do with ethics?' and answers 'it gives only part of the picture and so distorts our views on what is the best treatment for patients' [43].

There is now, within the DoH, a recognition that the publication bias which results from the propensity to publish 'positive' results at the expense of 'negative' results has the potential to harm patients and thus carries with it ethical obligations. The difficulty however, remains that publications seek to maintain their readership and that publishing positive results which may change the course of medical practice is widely perceived as more interesting than negative results which would tend to favour the *status quo*. It is possible that the internet may provide at least a partial solution and that negative results which would otherwise be unpublished may be made publicly accessible through the World Wide Web. The issue of electronic 'open access publishing' has recently been debated [44]. One point of contention surrounds who pays for such publication, and the recently launched Public Library of Science charges authors for publication. Lacking completely in the debate in this recent article, however, is what effect these changes may have on the publication of negative results and avoidance of publication bias. Therefore, it still remains unclear whether the aspirations of paragraph 27 will be achieved in practical terms.

Other changes

As pointed out above, the 2000 revision of the DoH left very few paragraphs unchanged. The changes not commented on in detail are listed in Table 3. The fact that we have not commented in detail is not an indication that the changes are considered unimportant, but rather that their introduction seems to have caused little controversy. Our discussion therefore now proceeds to consideration of possible future trajectories for the DoH.

The Declaration of Helsinki: future

There is little doubt that the influence of the DoH remains a central guide to research practice. This is illustrated, at least in part, by the use of the Declaration by other important documents pertaining to research ethics [45]. The Council for the International Organizations of Medical Sciences (CIOMS) guidelines on research ethics, for example, include the full DoH as an appendix and make extensive reference to the DoH in the text. In the longer term, it may be that the influence becomes 'diluted' by the confusing proliferation of international guidelines, codes of practice and other instruments such as those recently developed by CIOMS, by the International Conference on Harmonization (ICH) and by the Council of Europe. However, none of the above is really of the same genre of document as the DoH. Each is much lengthier, and attempts to cover questions of what to do in particular practical situations. The DoH, on the other hand, seeks to articulate a basic set of principles, to function as a code of ethics.

Therefore, it could be argued that the main influence of the DoH is not so much in answering specific questions about certain ethical protocols – although some of

Table 3
Other significant changes to the text of the Declaration of Helsinki in the 2000 revision (see Appendix 2 for full text of Declaration of Helsinki)

Paragraph number	Subject of the changes
8 (new paragraph)	Research on people from vulnerable groups
13 (modified paragraph) committees	Ethics committees have the right to monitor research; disclosure of potential conflicts of interest to ethics
16 (modified paragraph)	Design of all studies to be publicly available
21 (modified paragraph)	Explicit mention of protection of confidentiality of information about the patient
22 (modified paragraph)	Provisions where consent cannot be obtained in writing
25 (modified paragraph)	'Consent' changed to 'assent' with respect to research involving children
26 (new paragraph)	Provisions where consent from subject not possible
31 (modified paragraph)	Requirement to fully inform patient what aspects of their care relate to the research
32 (new paragraph)	Use of unproven techniques to save life or re-establish health should be made the object of research and the results recorded and published where appropriate

its paragraphs are certainly useful in that regard – but rather the DoH is part of the foundation on which these more detailed guidelines have been drafted.

There are a number of other trends which need consideration in terms of the future of the DoH. Probably the most important underlying question, however, is 'from where does the DoH draw its authority?' We consider four possible sources for this authority.

The World Medical Association (WMA)

One possible answer is that it draws its authority from being a Declaration of the WMA. This is the largest global grouping of doctors and as such there may be legitimacy in the claim that it is an authoritative body for making statements about the collective views of the medical profession.

However, one historical observation would seem to undermine any argument that this explains the authority of the DoH. Arguably the Declaration's period of greatest acceptance as an authoritative document dates in the period from the late 1970s (after the 1975 amendment had been widely promulgated) to the mid–late 1990s when increasing calls for modification to the DoH began to be voiced. However, this was a period of considerable internal turmoil for the WMA. In the 1980s, several countries (the so-called 'Toronto Group'), including the UK, withdrew from the WMA over ongoing objections to the refusal of the South African Medical Association to condemn apartheid. The events of history have allowed reconciliation of this rift and all of the breakaway countries had rejoined the WMA by 1995 [46].

This, we believe, calls into question any conclusion that the DoH's authority rests solely, or even largely, on the nature of its 'author'. It may even be that as the WMA strengthens and enlarges it will be more difficult to obtain consensus on documents such as the DoH, and particularly on difficult paragraphs such as 29 and 30.

The Declaration's succinctness

Although there is also clear evidence of a trend toward the DoH becoming longer (see Figure 1), there is no doubt that the Declaration – still less than 2000 words in length – is one of the most succinct documents encapsulating the principles guiding research ethics in existence. It can be read from beginning to end in less than 10 minutes.

On the one hand, the increasing complexity of research issues means that it is hardly surprising that a lengthening has occurred. On the other hand, the question must be asked: How much has its succinctness helped to establish its authority? If this is a major basis for the DoH's influence then the increasing length of the document, and the use of 'clarifications', must be a matter of great concern.

The Declaration's long-standing pre-eminence

There is an apparent tendency toward the DoH being changed more frequently (see Figure 1). However, it must be recognized that only two of the revisions (1975 and 2000) were more than minor in nature. This means that the period between extensive revisions is 11 (from 1964 to 1975) and 25 (from 1975 to 2000) years, respectively. Therefore the DoH, essentially in its 1975 form, had a quarter of a century to become embedded in the medical research community, and this may contribute significantly to the position it has come to occupy. On the other hand, there is recognition of the need to update the document to recognize the changing world of biomedical research [15]. Finding the correct balance between the need to modernize the document and the necessity to allow the text to become familiar within the medical research community will be important to maintaining the status of DoH.

It should be pointed out that the delegates to the World Medical Assembly are well aware of these trends toward lengthening of the document and more frequent changes. A previously published version [47] of Figure 1 was presented during the President's opening address of the Scientific Session of the most recent World Medical Assembly in Helsinki [48].

The Declaration has successfully articulated more broadly accepted principles

Did the DoH achieve its authority because it accurately articulated deeply held and broadly based ethical principles regarding the ethics of medical research? Almost like an ancient religious text, where commentaries debate the meaning of individual words, the DoH is the subject of almost a word-by-word analysis. Consider Article 29, where an enormous amount of ink has been spilled over the meaning of 'best current'. The Nuffield Council Document on 'Research in Developing Countries' devotes an entire chapter to what is effectively a debate about the true interpretation of this phrase [49].

If this is the basis of the Declaration's authority then the relevant question is whether the Edinburgh (2000) revision represents a superior expression of these deeply and widely held values to that of its predecessors.

Only time will tell what is the correct answer regarding the future of the DoH. However, it is worth reflecting on the following: when controversies arise, such as those surrounding paragraphs 29 and 30, there really are only three broad reasons which may underline such controversies.

First, if the wording of the document is at odds with the true underlying ethical principles then they must be better articulated, i.e. better 'word-smithing' is the way forward. Second, it may be that there really is no universal consensus about the ethical issues at stake, in which case some kind of 'agreement to differ' would be the only way to achieve a consensus document.

A third possible reason for a flurry of controversy over the wording needs to be considered. Has the document shone an uncomfortable light on practices which are questionable ethically? In this last regard, bioethicist H. Tristram Englehardt [50] speaks of the potential offensiveness of ethics. Aspects of his discussion could be paraphrased along these lines; to say someone is in the wrong *factually* has the potential to create a certain degree of offence, but to say that someone is in the wrong *ethically* is to criticise at a much deeper level and may cause a much more profound level of offence. If the reason for the controversy over statements such as paragraph 30 is that the text of the DoH has made parts of the research community feel very uncomfortable about the ethics of certain types of research, then it is important that the guiding principles not be amended or diluted through notes of clarification, but rather it is the behaviour of the research community which needs to change.

Concluding remarks

In compiling this review, we have sought to familiarize readers with the evolving text of the DoH over its nearly half-century of existence. We have raised what we see as important issues regarding its future, but up to now we have avoided one important question. Since time immemorial the medical profession has used codes of ethics to sum up the ethical responsibilities members of the profession take upon themselves in the practice of medicine. Undoubtedly the best known of the ancient codes is the Hippocratic Oath [51]. With respect to ethical codes in medical research the Nuremberg Code and the DoH hold pride of place. The unanswered question is whether the existence of such codes really raises the ethical standards in medical research or whether they are 'Only words, words; to be led out to battle against other words?' [52]. The fact that a supposedly rigorous code of medical research ethics existed in Germany from 1931 through to the end of the Second World War [53] raises this question rather starkly and has led Weisstub to caution: 'We should not be naive about the capacity of codes or legislation to bring unanimity and predictability to the subject' [54].

Yet there is little doubt that promulgation of the Edinburgh (2000) revision of DoH has sensitized the medical research community to many important issues once again. On the one hand, some may question the value of a document that aspires to such a high ethical standard. On the other hand, it must also be of considerable interest to note the responses of a researcher or an organization to these aspirations. A very interesting question which deserves much greater consideration is to ask just what is revealed when the response to the text is to seek loopholes and ask 'what can I get away with?', as opposed to 'How can I seek to achieve these aspirational standards in my research?'.

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Appendix 1: The Nuremberg Code (1947)

The judgement by the war crimes tribunal at Nuremberg laid down 10 standards to which physicians must conform when carrying out experiments on human subjects.

1 The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent, should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment. The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs, or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.
2 The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3 The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results justify the performance of the experiment.
4 The experiment should be conducted as to avoid all unnecessary physical and mental suffering and injury.
5 No experiment should be conducted where there is an *a priori* reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.
6 The degree of risk to be taken should never exceed that determined by humanitarian importance of the problem to be solved by the experiment.
7 Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability or death.
8 The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct and engage in the experiment.
9 During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
10 During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of good faith, superior skill and careful judgement required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

Appendix 2: Declaration of Helsinki (1975)

Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan October 1975.

Recommendations guiding medical doctors in biomedical research involving human subjects.

Introduction

It is the mission of the medical doctor to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the doctor with the words: 'The health of my patient will be my first consideration', and the International Code of Medical Ethics declares that 'Any act or advice which could weaken physical or mental resistance of a human being may be used only in his interest'.

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies *a fortiori* to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects. In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research the essential object of which is purely scientific and without direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research purposes must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every doctor in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Doctors are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

Basic principles

1 Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific tradition.

2 The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance.

3 Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given her consent.

4 Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5 Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interest of science and society.

6 The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7 Doctors should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Doctors should cease any investigation if the hazards are found to outweigh the potential benefits.

8 In publication of the results of his or her research, the doctor is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9 In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The doctor should then obtain the subject's freely given informed consent, preferably in writing.

10 When obtaining informed consent for the research project the doctor should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case informed consent should be obtained by a doctor who is not engaged in the investigation and who is completely independent of this official relationship.

11 In cases of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with the national legislation.

12 The research protocol should always contain a statement of ethical consideration involved and should indicate that the principles enunciated in the present Declaration are complied with.

II Medical research combined with professional care (clinical research)

1 In the treatment of the sick person, the doctor must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers the hope of saving life, re-establishing health or alleviating suffering.

2 The potential benefits, hazards and discomfort of a new method should be weighed against the advan-

tages of the best current diagnostic and therapeutic methods.

3 In any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method.
4 The refusal of the patient to participate in a study must never interfere with the doctor–patient relationship.
5 If the doctor considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee.
6 The doctor can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III Non-therapeutic biomedical research involving human subjects (non-clinical biomedical research)

1 In the purely scientific application of medical research carried out on a human being, it is the duty of the doctor to remain the protector of the life and health of that person on whom biomedical research is carried out.
2 The subjects should be volunteers – either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3 The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.
4 In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

Appendix 3: World Medical Association Declaration of Helsinki (2000)

Ethical principles for medical research involving human subjects.

Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975.

35th WMA General Assembly, Venice, Italy, October 1983.

41st WMA General Assembly, Hong Kong, September, 1989.

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000.

Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002.

A. Introduction

1 The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2 It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
3 The Declaration of Geneva of the World Medical Association binds the physician with the words, 'The health of my patient will be my first consideration', and the International Code of Medical Ethics declares that 'A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient'.
4 Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5 In medical research on human subjects, considerations related to the well-being of the human subject should take preference over the interests of science and society.
6 The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7 In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8 Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally

from the research, and for those for whom the research is combined with care.

9 Research investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this document.

3. Basic principles for all medical research

10 It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11 Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12 Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13 The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14 The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15 Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16 Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17 Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18 Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19 Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20 The subjects must be volunteers and informed participants in the research project.

21 The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22 In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23 When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24 For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25 When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26 Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27 Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. Additional principles for medical research combined with medical care

28 The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29 The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

To clarify further the WMA position on the use of placebo-controlled trials, the WMA Council issued, during October 2001, a note of clarification on article 29.

30 At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31 The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient–physician relationship.

32 In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Note of clarification on paragraph 29 of the WMA Declaration of Helsinki

The WMA is concerned that paragraph 29 of the revised Declaration of Helsinki (October 2000) has led to diverse interpretations and possible confusion. It hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

Where for compelling and scientifically sound methodological reasons it is necessary to determine the effi-

cacy or safety of a prophylactic, diagnostic or therapeutic method; or

Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki nust be adhered to, especially the need for appropriate thical and scientific review.

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- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

RESEARCH ETHICS

The three official language versions of the Declaration of Helsinki: what's lost in translation?

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Background: The Declaration of Helsinki, the World Medical Association's (WMA's) statement of ethical guidelines regarding medical research, is published in the three official languages of the WMA: English, French and Spanish.

Methods: A detailed comparison of the three official language versions was carried out to determine ways in which they differed and ways in which the wording of the three versions might illuminate the interpretation of the document.

Results: There were many minor linguistic differences between the three versions. However, in paragraphs 1, 6, 29, 30 and in the note of clarification to paragraph 29, there were differences that could be considered potentially significant in their ethical relevance.

Interpretation: Given the global status of the Declaration of Helsinki and the fact that it is translated from its official versions into many other languages for application to the ethical conduct of research, the differences identified are of concern. It would be best if such differences could be eliminated but, at the very least, a commentary to explain any differences that are unavoidable on the basis of language or culture should accompany the Declaration of Helsinki. This evidence further strengthens the case for international surveillance of medical research ethics as has been proposed by the WMA.

One issue that has almost completely escaped mention in the debate on a global consensus on bioethical issues is the difficulty presented by linguistic barriers. Here we consider this issue in relation to the Declaration of Helsinki (DoH). This document has been central to the World Medical Association's (WMA's) efforts to achieve consensus on the ethical conduct of medical research and arguably remains the most important international document in this field.[1 2]

Reiterating the organisation's efforts, the Director of Ethics at the WMA, Dr John Williams, has recently issued the challenge that "every effort should be made to internationalise bioethics".[3] Indeed, the challenge of addressing differing ethical standards for research in different parts of the world formed one of the driving forces for the revision of the DoH in the first place.[4] That these issues are still a flashpoint for controversy is amply illustrated in a review of the film version of John Le Carre's novel *The Constant Gardener*, written by Marcia Angell, whose 1997 editorial (in *The New England Journal of Medicine*) helped ignite the controversy.[5] The book and film portray the fictional nefarious actions of a multinational pharmaceutical company. However, Angell uses the opportunity of the review to state again her concerns that medical research standards may differ between countries, and, in particular, that the standards of protection for research subjects are lower in developing countries, and that some researchers continue to exploit these lower standards to conduct studies that would not be ethically permissible in the sponsoring country.

In its most controversial paragraphs (paragraphs 29 and 30), the DoH has sought to address aspects of this issue. The ensuing uproar was such that 4 years of debate culminated first in the note of clarification to paragraph 29 in 2002 and later in the note of clarification to paragraph 30 in 2004.[6]

Yet it also stands to reason that if international statements of ethical standards vary in their content across different language versions, this will be an additional impediment to the achievement of consistent international standards. We raise this question with respect to the DoH primarily because of the document's international prominence and its controversial attempts to go to the heart of these continuing ethical controversies. It also should be pointed out that because the DoH is relatively succinct at less than 2000 words,[7] and exists in only three official languages (compare, for example, the European Union Clinical Trials Directive, which is much longer and must be translated into the 20 official languages of the European Union), it is a less unwieldy starting point for this analysis.

The DoH exists in three official versions, one in each of the official languages of the WMA (English, French and Spanish).[6 8 9] The WMA is the largest global grouping of medical professionals and currently numbers the National Medical Associations of more than 80 nations as its members.[10] Eventually, the DoH will be translated from the official versions into a multiplicity of different languages, and will then likely go on to influence the wording of many other documents, so internationally the stakes are high. The WMA gives no guidance on such further translation and it is up to the organisation that is arranging a translation as to which official version or versions to use as their baseline, and the accuracy of such further translations remains the responsibility of that individual or other organisation.

METHODS

We undertook a detailed comparison of the English, French and Spanish versions of the DoH. In each case, this was initially undertaken by doctors on our authorship team who grew up in contexts where they were fluent in both of the languages (NHG for the French–English comparison and LMP for the Spanish–English comparison) and who have used both of the relevant languages extensively in a professional context. To reduce the subjectivity involved in this process, we obtained three translations of each of the French and Spanish versions of the DoH into English. The translators were all language

Abbreviations: DoH, Declaration of Helsinki; WMA, World Medical association

Table 1 The three official versions of second sentence of paragraph 1

English[6]	French[8]	Spanish[9]
1. ... Medical research involving human subjects includes research on identifiable human material or identifiable data.	1. ... Celle-ci comprend également les études réalisées sur des données à caractère personnel ou des échantillons biologiques non-anonymes	1. La investigación médica en seres humanos incluye la investigación del material humano o de información identificables.

teachers and were not previously aware of the content of the DoH. These back-translations were used to verify the differences detected on initial analysis. Full texts of these translations are available through a separate internet link.[11]

RESULTS

A detailed comparison of the English, French and Spanish texts of the DoH reveals, not unexpectedly, many grammatical and stylistic differences between the versions. Although in many cases these changes were not dictated by rules of language syntax or any obvious aesthetic advantage, most differences did not affect meaning. For example, in paragraph 5, the English and Spanish versions state, "In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society". The French version reverses the syntactic logic; "In medical research on human subjects, the interests of science and society should never take precedence over the well-being of the human subject".

The main concern of our discussion, however, is the small number of paragraphs where something important seems to be "lost in translation". Here we outline five that we consider of particular importance.

(1) True opposites or a risky assumption? (paragraph 1)

The English and Spanish versions use "identifiable", whereas the French version states "non-anonymes" (non-anonymous) to define the kinds of studies using data or tissue samples that are covered by the DoH guidelines (table 1). Ethical dimensions regarding protection of privacy of personal information in epidemiological and tissue sample studies have long been an issue for debate, but the 2000 revision is the first occasion when the DoH has explicitly referred to such issues.[7 12] The question of an ethically relevant difference in meaning hinges around whether there is any difference between "non-anonymous" and "identifiable", or put another way, whether "identifiable" and "anonymous" are exact opposites of one another. Clearly, if the researchers know the identity of the research subject, then data are "identifiable". On the other hand, if all possible re-linking of data with the person providing the data has been eliminated, then data are "anonymous". What about the intermediate situation where a code held by a third party separates the identity of an individual from the data used by the researcher? These would seem to be "non-anonymous" in that, if the right steps were taken, individual and data could be re-linked. But are they "identifiable"? Certainly they are not identifiable to the researchers and this may be considered to be the ethically important point. So we see that a grey area emerges that could possibly lead to different interpretations of the French version from the Spanish and English versions. Given that "non-anonymous" would be perfectly acceptable in the English version (and "no anónimo" in the Spanish), or that "identifiables" would be a valid adjective to use in the French version, we argue that this difference is unnecessary under the rules of the languages concerned and introduces an unnecessary risk of an ethically relevant difference in interpretation.

(2) Whatever happened to "quality"? (paragraph 6)

Without explanation, the French version omits the word "quality" from the list of criteria by which medical methods should be evaluated (table 2). This is of particular concern because internal discussions subsequent to the adoption of the 2000 version of the DoH raised concerns that "safety" was not explicitly included in this list. It was concluded by the WMA's Medical Ethics Committee in May 2002 that "the aspect of safety is sufficiently addressed by the term 'quality', which is already mentioned in paragraph 6".[13]

(3) Three languages, three standards in the control arm? (paragraph 29)

This paragraph (table 3), along with paragraph 30 (discussed below), has been one of the most controversial in the DoH. Both of these paragraphs, after lengthy word-by-word debate about their meaning, have had notes of clarification appended to them. In paragraph 29, a major controversy relates to the appropriate standard of comparator in an active-control trial. Should it be the best available anywhere in the world or the best that was available to the population in which the trial was conducted?[14] The change from "best current" (English) to "best existing" ("mejores existentes" in Spanish) and "in use" ("en usage" in French) is arguably the most significant difference we discovered between the three versions. Although we recognise that there may be semantic overlap, the French "en usage" carries some implication of a localised availability. However, the 1996 French version used the word "courantes" ("current") in the paragraph dealing with placebo and the change to "en usage" paradoxically seems to move the translation further away in potential meaning. On the other hand, the Spanish version is suggestive of a universal standard of care for the control group. The debate over the standard of comparator arm is not fully resolved. In this paragraph, the difference between the three language versions illuminates the debate but, of course, does not resolve it.

Table 2 The three official versions of the second sentence of paragraph 6

English[6]	French[8]	Spanish[9]
6. ...Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality	6. ...Les méthodes diagnostiques, thérapeutiques et de prévention, même les plus éprouvées, doivent constamment être remises en question par des recherches portant sur leur efficacité, leur efficience et leur accessibilité	6. ...Incluso, los mejores métodos preventivos, diagnósticos y terapéuticos disponibles deben ponerse a prueba continuamente a través de la investigación para que sean eficaces, efectivos, accesibles y de calidad.

Table 3 The three official versions of the first sentence of paragraph 29

English[6]	French[8]	Spanish[9]
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. ...	29. Les avantages, les risques, les contraintes et l'efficacité d'une nouvelle méthode doivent être évalués par comparaison avec les meilleures méthodes diagnostiques, thérapeutiques ou de prévention en usage. ...	29. Los posibles beneficios, riesgos, costos y eficacia de todo procedimiento nuevo deben ser evaluados mediante su comparación con los mejores métodos preventivos, diagnósticos y terapéuticos existentes. ...

(4) Differing standards for use of placebo controls? (note of clarification to paragraph 29)

The English version, in the second of the two clauses defining acceptable conditions for the use of placebo where proven therapy exists, makes the requirement that there be no "additional risk of serious or irreversible harm" (table 4). In the French version, we find "des risques supplémentaires de dommages significatifs ou durables". "Durables", which translates most closely as "long-lasting", would seem to have a different meaning from "irreversible". The adjective "irréversible" is available in French, or the English could be changed to "long-lasting" depending on what the intent is. The Spanish version uses "irreversible". However, the ethical demand does need clarifying. If a harmful outcome of a study potentially lasted several years (but was eventually reversible), would that really be acceptable? Our suggestion is that it would not and therefore that either the French version is preferable, or all three versions should refer to "long-lasting or irreversible" in this paragraph.

(5) Requiring the impossible? (paragraph 30)

This paragraph (table 5) has also been the subject of considerable controversy and, in October 2004, had a note of clarification appended.[6 8 9] The English version calls for patients to be "assured of access", whereas the French requires that patients be "assured of benefit". This seems to be beyond what any ethical code can require. It is only the potential benefit (through assurance of access) that can be required. Perhaps a wording that combines the two versions could read "should be assured of access to the potential benefit of...". The note of clarification to paragraph 30, added in 2004, may partially address this problem by speaking of "access" (accès) rather than benefit, but the difficulty with the wording of the paragraph itself still stands.

"Must" or "should"?

Debate continues about whether normative ethical guidelines such as the DoH, which do not have the status of legal documents, are best seen as pragmatic (and thus able to be followed in every case) or as aspirational (thus setting the direction but recognising that not every case will achieve every aspiration). Interestingly, the versions may differ in this regard. The Spanish ("deber", and its conjugates, rather than the conditional "deberia") and French ("doivent" and its conjugate "doit" rather than "devrait") consistently use words more closely equating to "must". English, on the other hand, uses "should" 16 times and "must" 5 times where the Spanish "deber" and French "doit" are used. The one exception is paragraph 4 of the DoH where the English ("research ... must rest in part on...") is translated in French as "peuvent imposer de recourir" (ie, "may require recourse to..."). However, this sentence could be considered descriptive of a fact rather than a statement of an ethical guideline and thus is not a true exception to the statement above.

It is not possible simply by analysing the text to understand what to make of this, eg, whether the Francophone or Hispanophone worlds see a set of normative ethics differently from the Anglophone world. Nor is it clear why the English version switches between "should" and "must". Further conjecture is therefore beyond the scope of this paper. It remains, however, an intriguing difference that should be explored in further studies.

DISCUSSION

Guidelines for WMA translations are not published. However, both Dr Delon Human, the Secretary-General of the WMA at the time of the revision, and Dr John Williams, the current Director of Ethics at the WMA, affirm that the translations should be as close as possible to one another, recognising that some differences may be imposed by the syntactical rules or the cultural framework of the languages (Personal communications, 2004). Translation difficulties are an enormous communications challenge faced by any establishment dealing with people who speak different languages, and the WMA is no exception. We accept that there are complex philosophical and linguistic questions about the nature of language, translation and meaning that remain among the biggest issues in contemporary philosophy.[15 16] Steiner asserts, "each human language maps the world differently".[17] This is a simplified statement of a well-recognised theory within the study of linguistics and anthropology known as the Sapir-Whorf hypothesis, which contends that culture and ethics are so bound up in the language used that they can only be fully understood from within that linguistic system.[18] To the extent that this is true, not only will the translations always contain differences, but also some differences will never be apparent to those trying to investigate them.

On the other hand, as Peter Kay has pointed out, cultural differences may be much more significant than linguistic differences and may lead to very different world views between speakers of the same language.[19] This is especially relevant in view of the worldwide distribution of the three official WMA languages: Spanish would be an important language for ethical discourse in settings as diverse as Madrid, Montevideo and Havana, French in Port-au-Prince, Paris and Montreal, and English in Glasgow, Gabarone and Auckland.

Table 4 The three official versions of the relevant portion of the note of clarification to paragraph 29

English[6]	French[8]	Spanish[9]
...where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.	...lorsqu'une méthode prophylactique, diagnostique ou thérapeutique est mise à l'essai pour une affection bénigne et que la participation à l'essai n'expose pas à des risques supplémentaires de dommages significatifs ou durables.	...Cuando se prueba un método preventivo, diagnóstico o terapéutico para una enfermedad de menos importancia que no implique un riesgo adicional, efectos adversos graves o daño irreversible para los pacientes que reciben el placebo.

Table 5 The three official versions of paragraph 30

English[6]	French[8]	Spanish[9]
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.	30. Tous les patients ayant participé à une étude doivent être assurés de bénéficier à son terme des moyens diagnostiques, thérapeutiques et de prévention dont l'étude aura montré la supériorité.	30. Al final de la investigación, todos los pacientes que participan en el estudio deben tener la certeza de que contarán con los mejores métodos preventivos, diagnósticos y terapéuticos probados y existentes, identificados por el estudio.

Some might argue that there is no empirical evidence for differing standards as a result of these translation issues within the DoH. We invite those who would contend this to consider both the difficulty in gathering such evidence (given linguistic difficulties), the long time-frame before those differences would be noticed empirically, and most importantly to consider whether we really want to find out about such systematic differences after the fact.

It is by no means our intention to suggest that any of the three official languages should become dominant in determining the wording of the DoH, or in any other debate regarding issues of international importance in medical research ethics. One of the major drawbacks of our study is that analysis of the results has been in English only. Ultimately, in the absence of a universal language, there is no way around the fact that discussions of meaning must take place in one language or another. The use of English is dictated by the provenance of this work.

The existence of discrepancies that could lead to a difference in interpretation is worrying. That we have demonstrated the existence of such discrepancies in the case of the relatively succinct DoH, across only three languages, gives rise to questions about other key international documents that are longer and have many more official language versions. So what is to be done?

In the first instance, the WMA should address these differences either by way of explanation or by way of the necessary amendments to the DoH to harmonise their meaning. Given the intense word-by-word debate and analysis that occurs both in WMA meetings and in the subsequent literature about the DoH, attention to these differences between the three official versions is vital. The DoH remains too significant an international instrument to leave these inconsistencies unattended.

On a broader note, however, this study shows one possible source of variation in ethical practice regarding research in different parts of the world. It raises the much bigger question of how to detect and act upon research standards that vary in unacceptable ways in different geographical settings (we accept that some variations, eg, greater emphasis on verbal consent than on written consent in different cultures, may be acceptable). One possible way forward was suggested by Dr Kgosi Letlape of South Africa, currently president of the WMA, when he made his speech as president-elect in Tokyo in October 2004. Dr Letlape mooted the creation of a surveillance unit to monitor coherence with the standards of research in various parts of the world.[20] Unfortunately, this aspect of his speech was neither reported in the written summary,[21] nor does it appear to have been taken any further by the WMA.

The last 50 years has seen the widespread recognition of two lines of defence for protection of people participating in research: voluntary participation through appropriate consent and the establishment of independent ethical review committees. What is lacking now, especially in the context of increasing multinational studies, is some system to ensure that standards worldwide do not fluctuate outside ethically acceptable parameters of variation. Dealing with the issue of linguistic harmonisation of ethical guidelines would ideally fit within the work of such a surveillance unit. However, harmonisation of the three official versions of the DoH need not, and should not, wait for its establishment.

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History and Theory of Human Experimentation

The Declaration of Helsinki and Modern Medical Ethics

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Table of Contents

Robert Carlson, Kenneth Boyd, David Webb

The Interpretation of Codes of Medical Ethics: Some Lessons from the Fifth Revision of the Declaration of Helsinki

I. Introduction

In this chapter we seek to summarise how the text of the Declaration of Helsinki (DoH) came into its current form. We will briefly describe the changes with the first four revisions from the original 1964 version and then consider in more detail the discussions leading up to the fifth and current revision of the Declaration of Helsinki. This revision has given rise to considerable controversy and we will focus on what are the three most controversial paragraphs (paragraphs 19, 29 and 30) in the current version. We make use of archival material made available by the World Medical Association (WMA) to trace in detail how these particular paragraphs evolved. By undertaking this analysis, we have the twofold aim of exploring in further detail the apparent ethical intentions behind these paragraphs and to consider what lessons this process may provide when the DoH, at some point in the future, is further revised.

II. The Evolution of Previous Versions of the Declaration of Helsinki

We have published elsewhere a detailed analysis of how the text of the DoH changed with each of the revisions and only a brief outline is provided here.[1]

II.1. The Original (1964) Declaration of Helsinki

In September 1964, the WMA officially published in its quarterly journal, the World Medical Journal, the text of the original DoH.[2] As with all Declarations of the WMA, the DoH was published in the three official languages of the organisation: English, French and Spanish. Although not officially published until September, the contents of the DoH were already widely available. For example, the British Medical Journal (BMJ), on 18 July 1964 contained the following very brief statement:

1 Carlson et al. (2004), pp. 695-713.
2 World Medical Association (1964).

> "A draft code of ethics on human experimentation was published in the British Medical Journal (BMJ) of 27 October 1962. [...] A revised version was accepted as the final draft at the meeting of the World Medical Association in Helsinki in June 1964. [...] It is to be known as the Declaration of Helsinki".[3]

This modest "birth announcement" in the BMJ belied just how important this document would become over the ensuing four decades.

Sev Fluss has undertaken a detailed comparison of the DoH with the Nuremberg Code of 1947 and notes the extensive influence of Nuremberg on the DoH.[4] In a detailed analysis, Herranz identifies within the Nuremberg Code's ten paragraphs, twelve statements that serve as markers to determine whether a particular medical experiment conformed to appropriate ethical standards. He noted that ten of these twelve markers from Nuremberg are retained in the DoH.[5] The original DoH, at just over 700 words in length, was a very brief document when compared with future (and the current) revision(s). Each of the subsequent revisions has added material and very little has been removed.[6] We now turn to a brief review of each of the earlier revisions.

II.2. The First Revision: Tokyo (1975)

In proportionate terms, this was the most substantial of all the revisions (including the present revision) of the DoH. The length of the document nearly doubled. This revision was the work of three Scandinavian professors of medicine[7], one of whom, Professor Povl Riis, remains very active in academic commentary on codes of ethics pertaining to medical research[8] and has contributed one of the chapters to this volume.

Given the very minor nature of the second, third and fourth revisions (see below), it is reasonable to assert that it is this – the 1975 version – that became the form of the DoH that rose to prominence in the medical research community over the next quarter-century.

Since the focus of this chapter is the fifth (Edinburgh, 2000) revision we only briefly review the changes in 1975. Arguably the most far-reaching practical development in the 1975 revision was the introduction of a paragraph outlining the requirement that research protocols be submitted to an independent committee for review prior to the conduct of the research (paragraph I.2 under the heading "Basic Principles"). Also new in the 1975 version was the important statement of the principle that the well-being of the participants in research must outweigh considerations of the benefit that the knowledge gained through the research may provide for "science and society". This is stated initially in a "positive" grammati-

3 Anonymous (1964), p. 177.
4 Fluss (1999), pp. 18-21.
5 Herranz (1998), pp. 127-139.
6 Carlson, Boyd and Webb (2004), pp. 695-713; see Figure 1.
7 Flanagan (1997), p. 926.
8 Riis (2000), pp. 3045-3046.

cal format in the "Basic Principles" section: "Concern for the interests of the subject must always prevail over the interest of science and society". It is restated (in its opposite grammatical format) in the section pertaining to "Non-therapeutic biomedical research involving human subjects (Non-clinical research)": "In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject".

II.3. The Second Revision: Venice (1983)

This was a minor revision in comparison to the extensive remodelling of the DoH undertaken in 1975. Apart from the essentially cosmetic changes (the word "doctor" was replaced by the word "physician" and the Latin phrase "a fortiori" was replaced by "especially"), a paragraph was added regarding the issue of research on minors. Where a minor was capable of giving a degree of consent, then that consent for research participation was to be obtained in addition to the consent of the legal guardian.

II.4. The Third Revision: Hong Kong (1989)

This, along with the fourth revision, is one of the most minor of all the revisions. Although the actual number of words added was greater in this revision than in the fourth revision (29 words versus. 19 words in the fourth revision), the fact that the fourth revision changed a paragraph that was at the heart of one of the most controversial aspects of the DoH leads me to this assertion.

In the third revision, additional detail was added to the paragraph stating the requirement for independent review. The paragraph now specifies further the nature of the independence of the committee reviewing the research protocol and makes explicit the requirement that the committee must conform to the laws of the country in which the review takes place. The WMA does not publish any formal commentary to accompany the paragraphs or revisions and in this case it is perhaps regrettable because it would be interesting to know why this amendment was deemed necessary. This paragraph (now paragraph 13 in the Declaration of Helsinki) has been retained in the current version and is by far the longest and most detailed of the paragraphs. Arguably there is much redundancy. Given that the alternative is that a review committee might operate *outside* the law of the country, perhaps this should go without saying. Additionally, it could be argued that there is contradiction with the new paragraph 9 of the fifth revision whereby the requirements of the DoH are now stated to supersede any legal instruments that might have the effect of reducing the protections offered by the DoH. Up to the fifth revision, the DoH simply indicated a requirement that researchers be aware of and compliant with relevant legislation in addition to the ethical requirements of the DoH. By mentioning the fifth revision, we realise that we risk confusing the chronological structure of this chapter. However, we mention this

potentially very controversial issue here as some of the roots of it are highlighted by the 1983 revision. A detailed debate about this is beyond the scope of this chapter, but we will take the subject somewhat further in the later discussion of whether documents such as the DoH should be aspirational or prescriptive in nature.

II.5. The Fourth Revision: Somerset West, South Africa (1996)

As with the revision in 1989, the actual changes to the text in the fourth revision were minimal. Regarding the fourth revision, Williams observed: "Before 1996 there was no mention of placebos in the DoH. A strict reading [...] from the version in force in 1995 would seem to prohibit placebos altogether".[9] The only change in 1996 was to add the sentence shown below in italics to paragraph 3 in the section pertaining to "Medical Research Combined with Professional Care (Clinical Research)":

> "In any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method. *This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists*".

No change was made to the preceding paragraph II.2 which also relates to the standard of control to be used in research studies and which reads "The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods". Williams goes on to observe,

> "Throughout the recent revision process this [i.e. use of placebo] was one of the most contentious issues. It was exacerbated by revelations of placebo-controlled trials in developing countries where a standard treatment exists but is not widely available in those countries".[10]

This sets the stage well for a detailed consideration of the controversial paragraphs that emerged in the fifth (Edinburgh, 2000) revision of the DoH.

III. The Fifth Revision of the Declaration of Helsinki, Edinburgh, 2000.

The process for the fifth revision of the Declaration of Helsinki lasted from September 1997 to October 2000. It began with a submission by the American Medical Association (AMA) to the WMA Council and finally ended with the near unanimous adoption of the revised form of the Declaration of Helsinki at the WMA Assembly in Edinburgh, Scotland, in October 2000. The process essentially went through three major phases, the first two of which proved largely to be "false starts". It was decided in 1998 not to proceed with the version

9 Williams (2004), pp. 31-42.
10 Ibid.

proposed by the AMA but rather to convene a Working Group, chaired by Robert Levine of Yale University, to consider the proposed revision of the DoH. Once again, in 1999, the WMA decided against accepting the revision proposed and assembled a new working group in April 1999. This group comprised Nancy Dickey of the United States, Kati Myllymäki of Finland, and Judith Kazimirski of Canada.[11]

These three became colloquially known as the "three wise women" and it was their committee's deliberations that eventually provided the basis for the 2000 revision of the DoH. This Working Group reported to the Medical Ethics Committee of the WMA Council. The central focus of the analysis in the remainder of this chapter will be to consider the evolution of the text of what eventually became the three controversial paragraphs (paragraphs 19, 29 and 30) as the Working Group deliberated, reported to the Medical Ethics Committee (MEC), and received modifications based on the outcome of MEC and WMA Council meetings. To understand more fully the process, it is necessary to describe in further detail the operating procedures of the WMA and it is to this description that we now turn.

III.1. An Aside: World Medical Association Procedures for Drafting and Adopting Ethical Declarations

The process by which the WMA adopts Declarations has been described by Lurie and Greco as "quasi-democratic".[12] This is in contrast to a fully democratic, "one person-one vote" procedure. In this section, we aim to describe more fully the WMA's "quasi-democratic" process.[13] It is through this process that the text of the Declaration of Helsinki passed to take on its current form. To understand the process requires some understanding of the structure of the WMA.

To finally become a Declaration of the World Medical Association, a Declaration must be approved at the WMA's annual assembly. Annual assemblies are usually held in October of each year. The delegates to the annual assemblies are representatives of the constituent National Medical Associations (NMAs) that form the membership of the WMA.

Within the WMA there are six WMA regions: Africa, Asia, Europe, Latin America, North America and the Pacific. It is intended that the venue for the

11 Ibid.

12 Lurie/Greco (2005), pp. 1117-1119.

13 The WMA kindly invited one of us (Robert Carlson) to observe its medical ethics committee meetings, council meetings and annual assemblies throughout 2003 and 2004 while a note of clarification to paragraph 30 of the Declaration of Helsinki was under consideration. This description is based both on observations of these meetings and extensive discussions with WMA delegates and staff. We are grateful to John Williams, currently Director of Ethics at the WMA and formerly a Canadian Medical Association delegate to the WMA, for his helpful comments. These comments clarified many misperceptions on our part. The responsibility for any remaining inaccuracies rests with us.

annual assembly rotate through the six regions although for a variety of reasons, a strict order of rotations is not always followed. (For example, in 2001, the events of September 11 and the subsequent disruption to travel necessitated the cancellation of the planned annual assembly in New Delhi though the WMA Council did manage to meet at WMA Headquarters in Ferney-Voltaire, France.)

As mentioned above, regular members of the WMA are not individuals but the NMAs of the various member countries. It is possible for individual physicians to join the WMA as associate members. The associate members meet just prior to the Assembly and at this meeting they elect two representatives to the General Assembly. These representatives have the right to speak but not to vote.

There are eighty-one national medical association members (NMAs) currently listed at the WMA's website.[14] However, that does not mean that there are potentially eighty-one votes cast on any resolution at the annual assembly. Voting strength is weighted according to the "declared" number of members that each national medical association has. An individual national medical association can "declare" any number of members up to its actual number of members. The reason why an NMA would choose to declare fewer than its actual number of members is that the dues paid for WMA membership are linked to the number of declared members. Such an arrangement permits countries whose NMA has a relatively large membership (because of the large population of the country even taking into consideration the higher population: doctor ratio often observed in resource-poor countries) but has limited financial resources to "declare" fewer members. This allows some NMAs to participate in the WMA that would otherwise be unable to do so.

Individual NMAs must weigh the advantage of lower membership dues against the advantage of declaring the full number of members and receiving its full voting strength (and perhaps a place on the WMA Council – see below).

III.1.1. WMA Council

The WMA Council meets three times a year: usually in May at a venue near the WMA headquarters and in September or October, immediately prior to and immediately after the Annual Assembly. Although individual NMA members could, in theory, table a motion or resolution on the floor of the Assembly, the chances are very small that it would be accepted if it had not already been discussed and endorsed at a Council meeting (and the Committee stages – see below). Council meetings are both more frequent and longer, allowing much more scope for detailed debate than at the Annual Assembly.

Each of the six WMA regions must always have at least one representative from at least one of the six NMA regions. These regional representatives are elected for a period of two years at a time. Additionally, any NMA with 50,000 or more "declared" members (see above) is also entitled to a seat on the Council.

14 http://www.wma.net/e/members/list.htm.

Therefore, the Council tends to have more representation from countries with relatively large populations, whose NMAs are financially relatively well off.

III.1.2. The Medical Ethics Committee

There are three standing committees of the WMA: the Finance and Planning Committee, the Socio-medical Affairs Committee, and the Medical Ethics Committee. Membership of these three standing committees is drawn from the membership of the Council. Each of the three committees meets during Council sessions. With respect to the text of its Declarations, it is the job of the latter two committees to undertake the detailed "word-smithing" required and to bring to the full Council the recommended text of Declarations pertaining to socio-medical issues, or to medical ethics issues respectively. Where the Council cannot agree on the wording of a document, it will usually refer the document back to the relevant committee. In cases where there are deep divisions over the wording of a Declaration, or where a very important Declaration is put forward for major revision, an ad hoc Working Group may be formed that will draw up the text of a document for discussion, first at the Standing Committee stage and, subsequently at the Council stage. Such Working Groups will always canvass individual NMAs for their opinions. In some cases, including the revision of the Declaration of Helsinki, and the note of clarification to paragraph 30, the WMA will canvass opinion more broadly and invite comment from a wide range of experts whose interests impinge upon or are impinged upon by the text of the Declaration.

III.1.3. Voting Procedures

In both Council meetings and in the Standing Committees, each NMA member has one vote and a simple majority is required for resolutions to be passed. This situation changes completely at the Annual Assembly. Prior to the Assembly there is always a "credentialing" meeting. At this meeting, those NMAs who have paid the appropriate dues for the number of "declared" members are allocated their number of votes. Every NMA has at least one vote. For those with more than 10,000 "declared" members, an additional vote is allocated for each 10,000 "declared" members. Thus, for example, an NMA with 50,000 declared members would have six votes (assuming they had paid the appropriate membership dues by the time of the Assembly).

For resolutions at Assembly that do not relate to medical ethics a simple majority of these allocated votes suffices for the resolution to pass. A resolution to adopt or amend any of the WMA's ethics documents requires 75 per cent or more of these votes.

To be revised in October 2000, the Declaration of Helsinki had to pass through all of the procedures described above. Voting at Council is done by a show of hands. At the Assembly it is done by a show of cards, each one printed

with the number corresponding to that delegation's voting strength. The particular voting decisions of NMAs are not officially recorded by the WMA. All we can be certain of is that the text of any revision of the Declaration of Helsinki received at least 75 per cent voting support although the decision to adopt the text of the Declaration has been described as "near unanimous".[15]

III.2. The Evolution of the "Controversial Paragraphs"

Most of the contention that arose out of the fifth (Edinburgh, 2000) revision surrounded three paragraphs – paragraphs 19, 29 and 30.[16] That paragraphs 29 and 30 raised a storm of controversy is evidenced by the WMA's unprecedented step of issuing notes of clarification to these paragraphs. Paragraph 19 was considered for a note of clarification but the final decision was that such a step was unnecessary. The final versions of these three paragraphs are as follows:

> "Paragraph 19: Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
>
> Paragraph 29: The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
>
> Paragraph 30: At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study".

It is our aim at this point to consider, based on the material that was available in the WMA archives, how these three paragraphs evolved through the process of drafting the text. This analysis is based on unpublished documents made available to me by the WMA. The WMA kindly allowed me free search of their archives. However, because of limited space, limited staff numbers and a recent relocation of the headquarters, the archives were not systematically filed. Some relevant documents appear to be no longer extant – at least in the WMA archives.

The series of documents available that tracked the evolution of the text are all entitled "Proposed Revision of the Declaration of Helsinki" and are serially numbered as follows: 17.C/WW1/2000, 17.C/WW2/2000, 17.C/WW3/2000, 17.C/WW4/2000 and 17.C/WW5/2000. From the minutes of the WMA General Assembly in Edinburgh, 2000 it became apparent that the version presented to the Assembly was 17.C/WW8/2000. This was unchanged in the Assembly so the text of 'WW8' corresponds to the actual text of the fifth revision of the Declaration of Helsinki. Documents 17.C/WW6/2000 and 17.C/WW7/2000 are not extant in the WMA archives and the possible reason for this is discussed below. Although the deliberations of the Working Group began in 1999, documentation of these

15 Williams (2004), pp. 31-42.
16 Ibid.

deliberations is unavailable. We begin therefore with the text of the proposed revision (17.C/WW1/2000) that was presented by the Working group to the Medical Ethics Committee at the WMA Council meeting in May 2000.

III.2.1. May 2000 – 17.C/WW1/2000

Paragraph 19: This paragraph was not yet in the proposed text.

> Paragraph 29: "24. In any medical study, every patient – including those of a control group, if any – should be assured of proven diagnostic and therapeutic methods. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.
>
> 23. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods".

Comment: This document had what eventually became paragraph 29 numbered as paragraphs 24 and 23. The order of occurrence of what were previously paragraphs II.2 and II.3 in the 1996 version has been reversed (and this accounts for the numbering 24. and 23. in this document). With respect to the wording, what is labelled here as paragraph 24 is very similar to the 1996 version that reads: "In any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists". The wording of what is labelled here as paragraph 23 is unchanged.

The only proposed change therefore at this stage was to require assurance of "proven ... methods" rather than the "best proven" method.

Paragraph 30: This paragraph was not yet in the proposed text.

This document was considered by the Medical Ethics Committee and changes were made. The next version (17.C/WW2/2000) was presented by the MEC to the WMA Council. This Council meeting was held shortly after the MEC during the series of meetings on 4-5 May 2000.

III.2.2. May 2000 – 17.C/WW2/2000

The text as proposed by the MEC to WMA Council was as follows:

> Paragraph 19: "Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research".

Comment: What eventually became paragraph 19 is now included in the proposed text. The documentation indicates that the text initially proposed by the MEC was "Medical research is only appropriate..." and the word appropriate was changed to "justified" during the MEC meeting.

In this document this paragraph is numbered paragraph 24a. Apparently it had originally been included as a preamble to the statement about placebo controls. It was subsequently separated from this statement and moved forward in the DoH to be in the section entitled "Basic Principles (for All Medical Research)".

> Paragraph 29: "24b. In any medical study, every patient – including those of a control group, if any – should be assured of proven effective prophylactic, diagnostic, and therapeutic methods.
>
> 24c. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists
>
> 23. The potential benefits, risks and discomfort of a new method should be weighed against the advantages of the best current prophylactic, diagnostic and therapeutic methods".

Comment: It can be seen that what entered these deliberations as paragraph 24 has emerged in three pieces, i.e., 24a, 24b and 24c. Paragraph 24a, as mentioned, was moved to a place earlier in the proposed text. 24b and 24c are still consecutive. The only change to the wording of 24b or 24c is the addition of the two words "effective prophylactic". The previous version therefore required assurance of "proven diagnostic and therapeutic methods". It was now proposed to require assurance of "proven effective prophylactic, diagnostic and therapeutic methods".

In what is labelled here as paragraph 23, the word "hazards" has now been changed to "risks" and the word "prophylactic" added so that the phraseology matches that of paragraph 24b.

Paragraph 30: This paragraph was not yet proposed in the text.

The above changes were then deliberated by the WMA Council and the ensuing text (17.C/WW3/2000) was approved for distribution by the Council to the various NMAs.

III.2.3. May-October 2000: 17.C/WW3/2000

Some minor changes were made to other portions of the proposed text but no changes were made to any of the texts described above under 17.C/WW2/2000. Thus, with respect to what eventually became paragraphs 19, 29 and 30,:there is no difference between WW2 and WW3 in the series of documents under consideration. It was the text of 17.C/WW3/2000 that was then released to the various NMAs and further comment invited. The Working Group along with the then Secretary General of the WMA, Delon Human, then met in August 2000 to consider the proposed revision in the light of these further comments. They presented the updated proposed text (17.C/WW4/2000) based on these deliberations and this text was to be considered by the MEC in early October prior to the pre-Assembly Council meetings.

III.2.4. October, 2000: 17.C/WW4/2000

> Paragraph 19: "24a. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research. The protocol presented to the review committee must include a realistic plan to deliver those treatments identified through such research to the populations from which the subjects have been drawn".

Commentary: This proposed paragraph now contains a newly drafted second sentence.

> Paragraph 29: "24b. In medical research, every patient – including those of a control group, if any – should be assured of the best proven prophylactic, diagnostic and therapeutic methods. This does not exclude the use of inert placebo in studies where no proven prophylactic, diagnostic or therapeutic method exists.
>
> 23. The potential benefits, risks and discomfort of a new method should be weighed against those of the best current prophylactic, diagnostic and therapeutic methods".

Commentary: What were previously paragraphs 24b. and 24c. have now been combined into one paragraph 24b. The word "effective" has been replaced by "the best" so that patients are now to be assured of "the best proven prophylactic, diagnostic and therapeutic methods". This in fact restores the wording (with the exception of the addition of "prophylactic") of the adjectival portion of the sentence to what it was in the 1996 version of the DoH.

In paragraph 23 the indicative pronoun "those" has replaced "the advantages". "Those" makes reference to "benefits, risks and discomfort". Interestingly, the logic of the previous form of the sentence would have required that the "potential benefits, risks and discomfort" of a new method were weighed only against "the advantages" of the existing method. This potential inconsistency had been present in the DoH since 1975.

Paragraph 30: There remains no mention of the issue that would eventually appear as paragraph 30 in the revised Declaration of Helsinki. We can see that it did not emerge completely de novo but rather appears to be a re-interpretation of the implications of the former 24b., i.e. "In medical research, every patient – including those of a control group, if any – should be assured of the best proven prophylactic, diagnostic and therapeutic methods". This is the version that was considered by the Medical Ethics Committee (MEC) in its deliberations just prior to the General Assembly in Edinburgh in October 2000.

III.2.5. October 2000: 17.C/WW5/2000

As mentioned above there is no trace of documents 17.C/WW6/2000, 17.C/WW7/2000 and 17.C/WW8/2000 in the WMA archives. However, as the minutes of the Assembly indicate 17.C/WW8/2000 was the version adopted by the WMA Council and recommended to the WMA General Assembly. Since no changes were made at the Assembly, we can conclude that WW8 was identical to the adopted text of the revised Declaration of Helsinki.

The MEC met for long hours in the days leading up to the General Assembly in an attempt to finalise the wording of the revision of the Declaration of Helsinki. Working documents were created very quickly at various points in the deliberations and changes were ongoing. The following indicates the status of the text of the three paragraphs under consideration according to the working document 17.C/WW5/2000.

> Paragraph 19: "24a. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research".

Comment: The proposed second sentence requiring a "realistic plan to deliver" treatments identified as beneficial to the population has been removed. This sentence has now reverted to exactly the same wording as proposed by the MEC to the Council in May (see WW2 above). This is also the exact wording of what became paragraph 19 in the revised DoH. Therefore we can conclude that even if the non-extant WW6 and WW7 contained any differences, they were restored to this text by WW8.

> Paragraph 29: "23. The potential benefits, risks and discomfort of a new method should be weighed against those of the best current prophylactic, diagnostic and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists".

Comment: This paragraph has been extensively restructured from the previous version. The entire sentence relating to "assurance of access" has been removed (and the issue of assurance of access now appears in what was to become paragraph 30 – see below). The sentence beginning "The potential benefits..." is unchanged from its earlier version but it has now been placed before the sentence beginning "This does not exclude...".

> Paragraph 30: "24b. At the conclusion of the study, every patient in the study should be assured of access to the best proven prophylactic, diagnostic or therapeutic methods identified by the study".

Comment: This is the first appearance, at this late stage, of what became the controversial paragraph 30. It was initially a re-wording of the sentence formerly seen as paragraph 24b (see above).

III.2.6. October 2000 – the Fifth Revision of the Declaration of Helsinki, Edinburgh, 2000.

Paragraph 19: Apart from the re-numbering of the paragraph from its interim number 24a to its final position at 19 – a task that could only be finalised when the wording of the Declaration was finalised – there was no change to this paragraph. Paragraph 29:

> "The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not

> exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists".

Comment: Between the working document 17.C/WW5/2000 and the final version of the revised Declaration of Helsinki the phrase "the potential benefits, risks and discomfort should be weighed against ..." was changed to "The benefits, risks, burdens and effectiveness of a new method should be tested against ...". This represents three changes: (i) the word "potential" is removed; (ii) the more metaphorical verb "weighed" (medical research does not usually involve actually determining the weight of the new treatment under investigation) is changed to the more literal "tested"; (iii) the word "effectiveness" has been added to the list of attributes of the new method that need to be tested against the existing method.

> Paragraph 30: "At the conclusion of the study, every patient in the study should be assured of access to the best proven prophylactic, diagnostic or therapeutic methods identified by the study".

Comment: Apart from finalising the paragraph number (see comment above), no changes were made from 17.C/WW5/2000.

IV. Lessons from the Fifth Revision of the Declaration of Helsinki

We have now traced in detail the evolution of the text of the three controversial paragraphs of the Declaration of Helsinki. It is time to reflect on some of the lessons that can be learned from this analysis?

1. How important is the original intent of the authors of the DoH? We have already observed the structure of the WMA. It is the largest global grouping of doctors. The efforts of the WMA represent a much sought-after international consensus as to what is and what is not ethically acceptable in the conduct of medical research. As such, ethical proclamations by this organisation must be taken seriously. Through this analysis, we can take steps to get closer to understanding the intent of the authors of this Declaration.

2. It must be remembered, however, that once the deliberations of the WMA become fixed in the text of the Declaration of Helsinki then the text can take on a proverbial "life of its own". Although the WMA have been very open and generous in allowing access to their meetings and archives, for the most part those who will read, interpret and apply the Declaration of Helsinki will not be party to these deliberations. Therefore, it is also important that the text can stand alone and be interpreted by its readers in such a way that there is an understanding of what the ethical guidelines established by the Declaration of Helsinki mean in actual research practice. The notion of whether the meaning of a text lies in its author's intent, in its reader's interpretation or, indeed, somewhere else, remains a complex and vexed philosophical problem. It is reasonable to assert that, despite this, it is certainly disingenuous to deliberately misinterpret the author's intent. For example, an overly literal interpretation of paragraph 19, requiring a reasonable likelihood of benefit to populations from which research subjects are drawn, could

lead to the conclusion that research on populations of "healthy volunteers" was ruled out. It seems, however, that the explicit mention of research in "healthy volunteers" (paragraphs 16 and 18) and "those who will not directly benefit" (paragraph 8) would mean that such an interpretation requires a deliberate decontextualisation and misinterpretation of the intent of the paragraph.

3. There are hazards involved in drafting a document "by committee". The sudden appearance of paragraph 30 seemed to have taken the medical research community by surprise. The great difficulty involved in developing a Note of Clarification (the process took 4 years compared with 1 year for paragraph 29) may be a reflection of the fact that the implications of this paragraph were not subject to the same process of consultation with NMAs and others that was the case for paragraphs 19 and 29. That being said, it should also be noted that even though paragraph 29 was deliberated in this way, it also gave rise to considerable controversy following the October 2000 revision of the Declaration of Helsinki. Certainly the introduction of a longer time period between the finalisation of a proposed form of its most important declarations and the final vote on these declarations in its General Assembly may avoid the turbulent and somewhat controversial process of adding a Note of Clarification.

4. There needs to be further thought given to whether the Declaration of Helsinki is essentially an aspirational document or whether it is a prescriptive document. Ruth Macklin raises this question without answering it:

> "Beyond these debates lies a deeper question about the nature of ethical guidelines. Should they be 'pragmatic' or 'aspirational'? Adherents of the view that statements such as the Declaration of Helsinki ... must be 'pragmatic' are likely to rely on current and past practices as a guide to what is possible. The pragmatists dismiss 'aspirational' guidelines as too lofty and, therefore, unrealistic. For their part, the 'aspirationists' tend to be reformers who judge past or current practices to be ethically insufficient to ensure that the highest standards for research apply everywhere ...".[17]

Philosopher Dorothy Emmet has considered in detail from several philosophical perspectives the value of what she terms a "regulative ideal": "To say that something is unrealisable is to speak with reference to a goal or standard which may be approached but which cannot be attained. Nevertheless, practice may be oriented towards it".[18] Essentially Emmet sees considerable value in the notion of setting out aspirational standards as giving a direction or orientation to practice.

With respect to the Declaration of Helsinki, the WMA seems not to have finally settled upon whether the guidelines are prescriptive or aspirational. The detail in paragraph 13 (pertaining to the function of independent review committees and, as mentioned above, the longest and most complex paragraph in the DoH) suggests a prescriptiveness. On the other hand, the far-reaching implications of paragraphs such as 19 and 30 have a more aspirational character.

At the same time the possibility that there is value in the ambiguity cannot be ruled out. The suggestion of prescription negates the aspirational nature of the

17 Macklin (2004), p.27.
18 Emmet (1994), pp. 2-3.

guidelines being used as a convenient excuse for not fully meeting the apparent requirements. On the other hand, ascendance of aspiration over prescription means that research that is correctly oriented and moving in the "right direction", but not fully "there yet", will not be excluded.

V. Summary

In summary, we have traced very briefly the first to the fourth revisions of the Declaration of Helsinki. This set the stage for a detailed consideration of the process by which three of the most debated paragraphs of the fifth (Edinburgh, 2000) revision of the Declaration of Helsinki were formulated. In doing so, we described the relevant operating procedures of the WMA and then tracked the relevant portions of the proposed revision through these procedures. The aim of this exercise has been to illuminate further the process of "authorship" of the Declaration of Helsinki. To the extent that understanding the intent of the author is necessary in understanding the meaning of a text, it is hoped that this exercise provides additional insight into the potential ethical implications of the fifth revision of the Declaration of Helsinki.

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